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DIAGNOSIS AND TREATMENT OF GOUT AND GOUTY ARTHRITIS

PHILIP S. HENCH, M.D.

ROCHESTER, MINN.

Contrary to general belief, gout is fairly common in the United States; but it is frequently unrecognized. Most patients with gouty arthritis have their disease for several years and endure a number of attacks before a correct diagnosis is made.[1] This is unfortunate because, of the various articular diseases, acute gouty arthritis is one of the most responsive to treatment. Hence the most important point in the treatment of gout and gouty arthritis is its recognition. The diagnosis of gout must therefore be considered in some detail.[2]

Gout is a disease of unknown etiology characterized chiefly by (1) arthritis, which is at first acute and recurrent, each attack being followed by complete symptomatic remission, but which later tends to become chronic; (2) supposed abnormality in the renal excretion of uric acid, the end product of purine metabolism; (3) hyperuricemia, which is usually transient at first but later generally becomes chronic; (4) eventual deposits of sodium urate crystals in articular, periarticular and subcutaneous tissues, sometimes also in kidneys and urinary tract; (5) frequent terminal vascular lesions in the kidneys, sometimes also in the heart and brain.

Recent opinions [3] are that gout results from (1) some endocrine deficiency, (2) abnormal renal insensitivity to urates, (3) selective renal insufficiency for urates alone, (4) a "storm in the vegetative nervous system," a functional disturbance involving the renal or the thoracic sympathetic nerves, or (5) an allergic reaction to proteins, not necessarily to exogenous proteins derived from foods rich in purine (fig. 1), but also to proteins from certain nonpurine foods as well as to endogenous proteins, tissue substances formed after injuries, vasomotor disturbances or operations.

Gout and gouty arthritis are not synonymous; the latter is merely the dominant symptom of gout. The arthritis and the other principal features of gout (hyperuricemia, tophi, late renal and cardiovascular complications) are only the outward signs of some underlying chemical or metabolic abnormality of which little is known. This disturbance, the gout per se or the constitutional gouty state, is in symptomless operation for some time before acute arthritis first appears, and it is this fundamental abnormality which under suitable provocation gives rise to the subsequent appearance of the classic symptoms.

THE PATTERN OF GOUTY ARTHRITIS; ITS RELATION TO OTHER FEATURES

Gout can best be studied by noting the relationship of its other features to the pattern of gouty arthritis (fig. 2). The larval stage of gout is that period of the disease prior to the first attack of gouty arthritis. During this stage of gout the body is being unobtrusively conditioned for subsequent events, but little is known about the chemical or histologic abnormalities which are then transpiring. This larval or prearthritic stage of gout is generally, but not always, symptomless; sometimes it is accompanied by transient but definite hyperuricemia of varying intensity, and in a few cases it is characterized by the appearance of subcutaneous tophi or of renal urate stones or gravel, tophi of the urinary tract, which may be discovered even before the first articular attack.

The first attack of acute gouty arthritis sometimes occurs in a young person but usually affects persons, generally men, who are more than 35 or 40 years of age; it appears suddenly, lasts from three to ten or more days and then disappears completely. In about 60 per cent of the cases [1] it affects a great toe (podagra), but it may affect an instep, ankle, knee or other peripheral joint, and the great toes may long be unaffected. Therefore a diagnosis of gout must not be discarded just because podagra is absent. The second attack usually occurs after a year or so and may affect the joint previously involved or a new one; it may or may not be more severe and last longer than the first attack, and it also disappears completely. Sooner or later the tempo and severity of the disease generally increase; attacks may come semiannually (often in spring and fall) or more frequently. Early attacks are generally monarticular and afebrile; later attacks are often polyarticular and may be febrile (temperature of 102 F. or more). Although certain roentgenologic changes may appear and remain after several acute attacks, in the first stage of the disease joints recover full symptomless function.

From three to forty (average twelve) years after the first attack the second great stage of articular gout occurs, that of chronic gouty arthritis, when the joints no longer recover completely but some stiffness, pain or deformity remains; in this stage acute exacerbations are superimposed on the residual chronic gouty arthritis.

From the Division of Medicine, the Mayo Clinic.

1. Hench, P. S.; Vanzant, Frances R., and Nomland, Ruben: Basis for the Early Differential Diagnosis of Gout: A Clinical Comparison of 100 Cases Each of Gout, Rheumatic Fever and Infectious Arthritis. Tr. A. Am. Physicians **43**: 217-229, 1928.

2. Hench, P. S.: The Diagnosis of Gout and Gouty Arthritis, J. Lab. & Clin. Med. **22**: 48-55 (Oct.) 1936; Chronic Arthritis; [3] A Clinic on Some Diseases of the Joints; [6] Comments on the Diagnosis and Management of Gout in Certain Parts of the United States.[16] Hench, Vanzant and Nomland.[1] Hench and Darnall.[4]

3. Hench, P. S.: Chronic Arthritis: Chronic Infectious Arthritis, Chronic Senescent Arthritis, Gout, in Modern Medical Therapy in General Practice, Baltimore, Williams & Wilkins Company, 1940, pp. 3359-3384.

Thus the pattern of classic gouty arthritis can be divided into two great stages comprising four phases (fig. 2). Stage 1 is that of acute recurrent gouty arthritis; stage 2 is that of chronic gouty arthritis. Phase 1 of stage 1 is that of the early, less severe and generally monarticular attacks. In this phase hyperuricemia is often present but is frequently absent not only between but during acute attacks. Subcutaneous tophi and areas of erosion in roentgenograms which are indicative of osseous tophi are almost always absent in this phase and should not be expected. Phase 2 comprises the later, generally more severe and longer attacks, which may be febrile, are often polyarticular and are associated with a more definite and persistent hyperuricemia but are still followed by complete symptomatic remissions. In this phase subcutaneous and osseous tophi are more frequent but still present in only about 25 to 35 per cent of the cases.

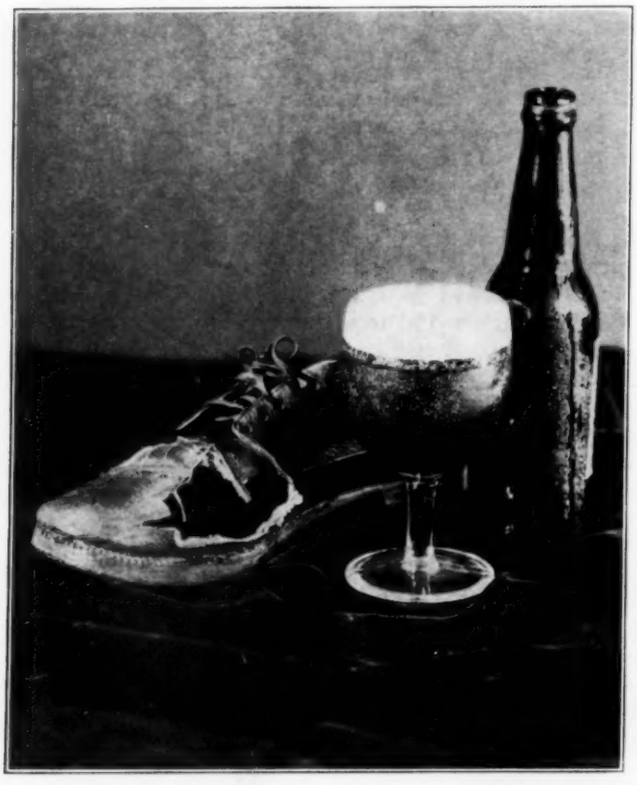


Fig. 1.—At the sign of a split shoe suspect gout. Excesses of alcoholics and purines are not the cause of gout, but they may cause acute gouty arthritis, the dominant symptom of gout.

In phase 3, which is the first phase of stage 2, early chronic gouty arthritis with acute attacks and incomplete remissions appears. In this phase hyperuricemia is almost always present in untreated patients but may be made to disappear, at least temporarily, under proper treatment. In this phase subcutaneous tophi on the ears, elbows and around joints are almost always present and may be multiple and ulcerating, and osseous tophi of the hands or feet, but rarely elsewhere, are commonly present. Phase 4, the second phase of stage 2, is the final stage of the disease, characterized by a relatively painless chronic gouty arthritis; hyperuricemia and multiple tophi almost always are present.

When active gout develops early in life it may reach stage 2 in middle life, but when the first symptoms of gout develop in middle or late life it frequently does not progress to stage 2 and the patient may die of some unrelated condition, perhaps at normal expectancy.

Gouty nephritis (nephrosclerosis with urate deposits and foreign body reactions in renal parenchyma) and renal colic from urate gravel or stones (urinary tophi) rarely manifest themselves in phase 1, occasionally appear in phase 2, and are not uncommon in phases 3 and 4; they are present in about 10 to 20 per cent of the total cases of gout. Aside from these renal lesions the only other valid examples of visceral gout are found in the cardiovascular system; degenerative vascular disease may complicate late gout and cause death by coronary or cerebral vascular accidents. These vascular lesions are nonspecific and do not contain urates, but intracardiac tophi have been seen,[4] although they are rare. For reasons that have been given elsewhere[3] I have rejected the conception of irregular as opposed to classic gout.

DIAGNOSIS OF GOUT AND GOUTY ARTHRITIS

When a patient has had several attacks and has had the disease long enough for some of the so-called diagnostic features, podagra, hyperuricemia, subcutaneous and osseous tophi, to develop, the diagnosis should not be difficult even for physicians who are not particularly "gout conscious." Many absolutely typical cases, however, are not being diagnosed correctly by physicians who, never thinking of gout, fail to discover the hyperuricemia and tophi which are almost crying for recognition. Unfortunately for the early diagnosis of gout these "diagnostic features" do not appear in many, perhaps in most, cases until rather late in the disease. Indeed in some cases some of them never appear. Of any physician's total cases of gout in all stages subcutaneous tophi will be found in only about 50 per cent, areas of erosion as demonstrated in the roentgenogram in only about 30 per cent, and hyperuricemia in about 75 per cent.[1] Podagra will be found to be present at some time or other in about 80 per cent, but not necessarily in the first attack.

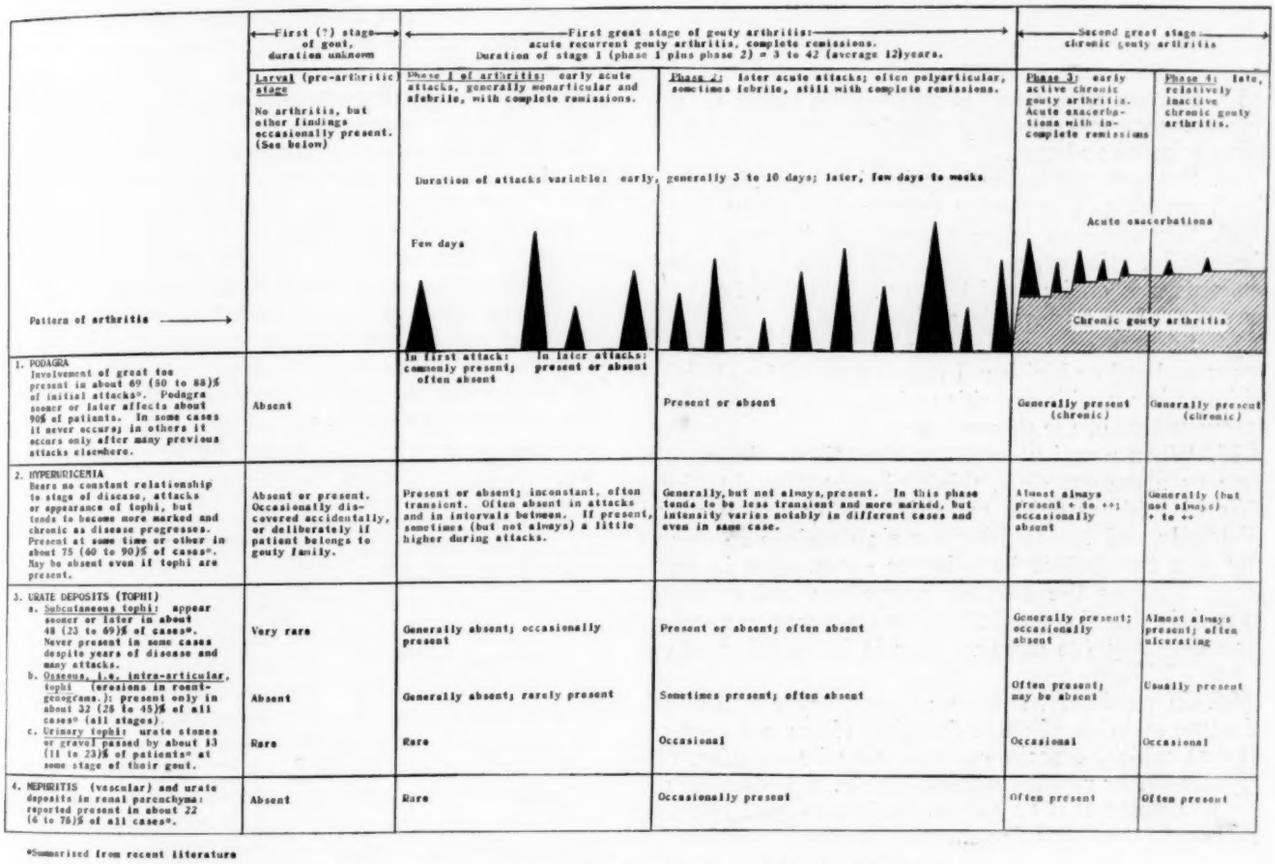
Physicians should not be content to postpone the diagnosis (and treatment) of gout until late in the disease when these "classic features" have become glaringly obvious. Without these features how can an early diagnosis be made? It can be made (1) during the first or any subsequent attack on the basis of certain features which are highly characteristic of the individual attacks or (2) after the second or later attack on the basis of the obviously developing characteristic pattern of gouty arthritis (fig. 2). This clinical pattern, which is made by acute recurring attacks and complete remissions, is so distinctive of gout as to be almost pathognomonic; it permits a diagnosis of presumptive or pretophaceous gout (in contrast to the diagnosis of tophaceous gout) with no little assurance, since it is not exactly mimicked by any of the other articular diseases which have recurrences and complete articular remissions; for example, rheumatic fever and intermittent hydrarthrosis.

Diagnostic Features of Individual Attacks.—When the patient is seen in the first or second attack with only a fragment of the clinical pattern in view, diagnosis is based on certain features, no one of which is diagnostic but a combination of which is almost pathognomonic for gout. Attacks which sometimes appear "spontaneously" commonly occur after some characteristic provocative, such as minor trauma or dietary indiscretion and less commonly after infection,

4. Hench, P. S., and Darnall, C. M.: A Clinic on Acute, Old-Fashioned Gout, with Special Reference to Its Inciting Factors, M. Clin. North America **16**: 1371-1393 (May) 1933.

surgical procedures, certain medicines and psychic upsets. Unaware of their significance, patients rarely mention these provocatives; they must be sought.[5] Attacks sometimes begin in the early morning hours but are usually noted when, on awakening, the patient puts the foot to the floor. In gout there is a gradient of articular vulnerability whereby the peripheral joints of the feet, ankles, hands and wrists are affected most often, the knees and elbows less often, the shoulders and hips rarely, and the spine very rarely if ever. Olecranon bursitis and achilles tendinitis often occur. When a great toe is affected, maximal tenderness is usually on its medial aspect, not on its top or bottom as in atrophic (chronic infectious, rheumatoid) arthritis. A gouty foot is more often warm and red or bluish

("exposition gout") or from long motoring (pedaling), or from excesses in golf or amateur laboring, for example, lawn mowing.[4] Post-traumatic gouty arthritis can be differentiated from true traumatic arthritis thus: True traumatic arthritis begins immediately after trauma; the inflammatory reaction is proportional to the severity of trauma, is confined to the traumatized region and is not relieved by colchicine; the characteristics of gout (history, hyperuricemia, tophi) are absent. In post-traumatic gouty arthritis the inflammatory reaction is often delayed some hours after trauma, is out of proportion to the amount of trauma experienced, often progresses to other nontraumatized joints and is relieved by colchicine; some of the characteristic features of gout may also be present.


First (?) stage of gout, duration unknown
First great stage of gouty arthritis: acute recurrent gouty arthritis, complete remissions. Duration of stage 1 (phase 1 plus phase 2) = 3 to 42 (average 12) years.
Second great stage: chronic gouty arthritis
Larval (pre-arthritic) stage
No arthritis, but other findings occasionally present. (See below)
Phase 1 of arthritis: early acute attacks, generally monarticular and afebrile, with complete remissions.
Phase 2: later acute attacks; often polyarticular, sometimes febrile, still with complete remissions.
Phase 3: early active chronic gouty arthritis. Acute exacerbations with incomplete remissions
Phase 4: late, relatively inactive chronic gouty arthritis.
Duration of attacks variable: early, generally 3 to 10 days; later, few days to weeks
Few days
Acute exacerbations
Chronic gouty arthritis
Pattern of arthritis
1. PODAGRA
Involvement of great toe present in about 60 (50 to 88)% of initial attacks*. Podagra sooner or later affects about 90% of patients. In some cases it never occurs; in others it occurs only after many previous attacks elsewhere.
Absent
In first attack: commonly present; often absent
In later attacks: present or absent
Present or absent
Generally present (chronic)
Generally present (chronic)
2. HYPERURICEMIA
Bears no constant relationship to stage of disease, attacks or appearance of tophi, but tends to become more marked and chronic as disease progresses. Present at some time or other in about 75 (60 to 90)% of cases*. May be absent even if tophi are present.
Absent or present. Occasionally discovered accidentally, or deliberately if patient belongs to gouty family.
Present or absent; inconstant, often transient. Often absent in attacks and in intervals between. If present, sometimes (but not always) a little higher during attacks.
Generally, but not always, present. In this phase tends to be less transient and more marked, but intensity varies notably in different cases and even in same case.
Almost always present + to ++; occasionally absent
Generally (but not always) + to ++
3. URATE DEPOSITS (TOPHI)
a. Subcutaneous tophi: appear sooner or later in about 48 (23 to 69)% of cases*. Never present in some cases despite years of disease and many attacks.
Very rare
Generally absent; occasionally present
Present or absent; often absent
Generally present; occasionally absent
Almost always present; often ulcerating
b. Osseous, i.e. intra-articular, tophi (erosions in roentgenograms.): present only in about 32 (25 to 45)% of all cases* (all stages).
Absent
Generally absent; rarely present
Sometimes present; often absent
Often present; may be absent
Usually present
c. Urinary tophi: urate stones or gravel passed by about 13 (11 to 23)% of patients* at some stage of their gout.
Rare
Rare
Occasional
Occasional
Occasional
4. NEPHRITIS (vascular) and urate deposits in renal parenchyma: reported present in about 22 (6 to 76)% of all cases*.
Absent
Rare
Occasionally present
Often present
Often present

*Summarized from recent literature

Fig. 2.—The basic pattern of gout and gouty arthritis (untreated).

red than clammy, cold and bluish white as in atrophic arthritis. Shiny skin, some edema and later desquamation of the skin often are notable. Attacks of gouty arthritis usually develop more rapidly than attacks of any other acute arthritis; maximal disability may appear within twelve to thirty-six hours. Pain may be moderate but is usually marked and is often excruciating; it may or may not be worse at night. Recovery may be slow but is generally (spontaneously) rapid, occurring within a few days, and in the first stage of the disease it is complete.

Diagnostic Features Summarized Axiomatically.—My diagnostic criteria of gout and gouty arthritis are expressed in twenty-one points, as follows:

1. Suspect gout when acute arthritis suddenly develops after relatively trivial trauma, such as a walk of unaccustomed length, that from excessive sight seeing

2. Suspect gout when acute arthritis develops after dietary excesses of holidays, birthdays, lodge night, conventions and the like.[4]

3. Suspect gout when arthritis develops acutely within the first week after any surgical procedure; acute postoperative arthritis is usually gouty.[6]

4. Suspect as gout an acute arthritis appearing after the trauma, exposure and dietary excesses (venison, meat, alcohol) of a fishing or hunting trip[4] (fig. 1).

5. Suspect as gouty an acute arthritis which recurs in the spring or fall. Attacks, however, may occur any time.

6. Suspect gout when acute arthritis begins between 2 and 7 a. m., but gouty arthritis may occur at any hour.

7. Suspect gout when acute arthritis occurs while a patient is being given liver extract for anemia, mersalyl

5. Hench and Darnall.[4] Hench.[6]

6. Hench, P. S.: A Clinic on Some Diseases of Joints: II. Acute Postoperative Arthritis: Its Identification; III. Acute Postoperative Gout: Its Treatment and Prevention, M. Clin. North America **19**: 551-583 (Sept.) 1935.

(salyrgan) for dropsy,[7] ergotamine tartrate (gynergen) for migraine, a ketogenic regimen, thiamine hydrochloride (vitamin B_1),[8] dehydrocholic acid (decholin)[9] or insulin (rarely).[10] These are the medicinal provocatives of gout.

8. Suspect as gouty the acute arthritis of patients with leukemia or polycythemia or other dyscrasias involving destruction of blood and liberation of nucleoproteins.

9. Be cautious about making a diagnosis of gout in females; gout rarely affects females but when it does so it affects them in the classic manner. About 95 to 98 per cent of cases of provable gout occur among males.

10. Suspect as gouty any acute arthritis which suddenly and spontaneously affects a man more than 40 years of age; among such persons gouty arthritis is the commonest type of acute arthritis, but it may affect young persons of either sex.

11. Suspect gout when acute arthritis comes on and produces maximal disability with dramatic speed, within a few minutes or hours.

12. Suspect gout when the pain of an acute, but short lived, arthritis is unusually severe; "the worst ever."

13. Suspect gout when a great toe is acutely, not chronically, affected, and especially when the maximal tenderness is on its mesial aspect. Podagra, however, may occur late or never in a given case.

14. Suspect gout when an acutely affected foot is warm and red or bluish red rather than cold and bluish white as in atrophic arthritis and when edema and later desquamation of the skin are present.

15. When a patient presents himself, wearing a split shoe or a cut-out shoe, think of gout (fig. 1). Feet affected with atrophic arthritis usually are involved bilaterally and the swelling therein develops so gradually that the patient buys larger shoes. But in acute gouty arthritis the swelling progresses and regresses so rapidly that the patient handles the temporary articular emergency (so often unilateral) by splitting an old shoe.

16. In particular, suspect as gout any single attack of acute arthritis of short duration (from one to three weeks) which, especially considering its severity, disappears rather rapidly and completely. So complete are the remissions that "a person subject to gout has won the race at the Olympic games during the interval of the disease."[11]

17. Consider any patient with chronic arthritis who has previously had (generally several) recurrent attacks of acute arthritis with complete remissions, to have gout until proved otherwise (fig. 2). Search for hyperuricemia and subcutaneous or osseous tophi, but if they are absent do not hesitate to make a diagnosis of "presumptive gout" at least to the extent of instituting a therapeutic test.

18. Since olecranon bursitis is several times commoner in gout than in any other disease, suspect gout in patients who have it or give a sought for history thereof.

19. When the shoulders, hips or spine are acutely or chronically affected, make a diagnosis of gout with great caution and only on the basis of unmistakable signs of gout and of gouty arthritis elsewhere. Such is the gradient of articular vulnerability in this disease that gouty arthritis affects the spine rarely if ever, the hips and shoulders rarely and generally only after previous attacks in more peripheral joints. Gout does not tend to produce a rheumatism of the torso.

20. Suspect gout in cases of acute or chronic arthritis in which there is a history or signs of renal colic (urate stones or gravel) or nephritis. Renal stones and nephritis affect about 10 per cent or more of gouty patients but rarely affect patients with atrophic, or hypertrophic (senescent, degenerative, osteo-) arthritis and then only coincidentally. It must be remembered that urate stones cast no roentgenographic shadows.

21. When periarticular or para-articular ulcers or fistulas are present, rule out gout. Ulcerating gouty tophi are now more common than ulcerating tuberculous fistulas of the joints.

Of all these points a characteristic history of the articular attacks is the most important for early and accurate diagnosis. When such a history is absent, therapeutic and provocative tests have indicated, in my experience, that gout is rarely if ever present, regardless of the presence of other features suggesting gout. Provocative tests performed by giving excessive quantities of purine, fats or both are only occasionally helpful in diagnosis. Much more reliable are therapeutic tests, for which colchicine in full doses is used alone or with other antigout measures.

TREATMENT

Prophylaxis.—Children and other relatives of gouty patients sometimes possess symptomless hyperuricemia.[12] Such hereditary candidates for gout should live moderately, avoid occupations permitting gastronomic overindulgence and avoid or undertake cautiously the various provocatives of acute gout.

Treatment of Acute Gouty Arthritis.—Patients who experience recognizable nonarticular prodromes (some note nausea, dyspepsia, polyuria or euphoria and a ravenous appetite) or warning articular twinges can sometimes abort the impending attack by taking a brisk cathartic and a few doses of colchicine (each dose $\frac{1}{100}$ grain, or 0.65 mg., every two to three hours). It is better to institute such a regimen needlessly for a false alarm than to permit an attack to become established. When the latter does happen, treatment includes the following measures:

Cathartic: A brisk cathartic, magnesium sulfate from ½ to 1 ounce (15 to 30 Gm.), solution of magnesium citrate from 6 to 12 ounces (180 to 360 cc.) or sodium phosphate from 4 to 8 Gm., supposedly will promptly evacuate provocative toxins; its use is empiric but apparently helpful.

Rest: Affected parts should be rested completely, preferably in bed, and protected from bedclothes by a light wooden or metal cradle. Weight bearing and activity should be avoided until pain and tenderness disappear; otherwise an exacerbation may result.

Heat or Cold: Simple hot water compresses reapplied every one or two hours are generally effective and often

7. Price, N. L.: Gout Following Salyrgan Diuresis, Lancet **2**: 22-23 (Jan. 7) 1939. Hench.[2]

8. Vorhaus, M. G., and Kramer, M. L.: Studies on Thiamine Chloride in Gout, Tr. Am. Therap. Soc. **38**: 109-115, 1938; Acta rheumatol. **10**: 8-11 (Dec.) 1938.

9. Bowers, J. M.: Gout, Northwest Med. **37**: 284-287 (Sept.) 1938.

10. Rabinowitch, I. M.: An Unusual Case of Diabetes and Gout, Canad. M. A. J. **19**: 682-686 (Nov.) 1928.

11. Aretaeus: The Extant Works of Aretaeus, the Cappadocian (translated by Francis Adams), London, the Sydenham Society, 1856, p. 365; Aretaeus, the Cappadocian, Edited by Herman Boerhaave, ed. 4, Leyden, 1735, p. 67 B.

12. Folin, Otto, and Denis, Willy: The Diagnostic Value of Uric Acid Determination in Blood, Arch. Int. Med. **16**: 33-37 (July) 1915. Jacobson, B. M.: The Uric Acid in the Serum of Gouty and of Non-gouty Individuals: Its Determination by Folin's Recent Method and Its Significance in the Diagnosis of Gout, Ann. Int. Med. **11**: 1277-1295 (Jan.) 1938. Talbott, J. H.: Serum Urate in Relatives of Gouty Patients, J. Clin. Investigation **19**: 645-648 (July) 1940.

preferable to dry heat. Compresses of magnesium sulfate or lead lotion are prescribed by some physicians, lotions of aconite, belladonna and chloroform by others. Sometimes cold compresses give the most relief.

Colchicine: Colchicine tablets, each 1/120 or 1/100 grain (0.53 or 0.65 mg.), should be given: two tablets initially and one tablet every two or three hours (in severe cases even during the night) until pain is relieved or some gastrointestinal disturbance, such as nausea or diarrhea, appears. Having once learned his toxic or "diarrhea dose," a patient in subsequent attacks may (or may not) be able to obtain a satisfactory effect without the toxic effect by taking one or two less tablets in a course. Colchicine is more consistently effective than the wine or tincture of colchicum (dose from 15 to 30 minims or 1 to 2 cc. every two to four hours), which sometimes deteriorates. Gouty patients should carry a few colchicine tablets for prompt use when necessary.

Narcotics: Until pain is controlled by colchicine and compresses, a dose or two of codeine (from ½ to 1 grain, or 0.032 to 0.065 Gm.) or morphine sulfate (from ⅙ to ¼ grain, or 0.01 to 0.016 Gm.) may be required.

Cinchophen and Substitutes for Cinchophen: Attacks are better controlled when cinchophen or a substitute for it is used to supplement other measures, especially if hyperuricemia is present. Cinchophen should be given during attacks thus: 7½ grains (0.5 Gm.) three or four times daily with the precautions noted later in this paper (alkali, carbohydrates, extra fluid).

Some physicians prefer to prescribe one of the following substitutes daily during the attack: neocinchophen from 5 to 7½ grains (0.3 to 0.5 Gm.) three times a day; sodium salicylate 20 grains (1.3 Gm.) four times a day or acetylsalicylic acid 20 grains (1.3 Gm.) three or four times a day. I agree with those who have noted that in some cases these substitutes are not completely effective and inferior to cinchophen;[13] but cinchophen or a substitute for cinchophen used without colchicine is also inadequate in some cases.[14]

Diet: The diet currently approved for acute gouty arthritis is free of purines and low in fats (the latter inhibits urate excretion), rich in carbohydrates, which increase urate excretion, and rich in purine-free proteins (milk, eggs, cheese). This diet minimizes the formation of exogenous urates and fosters elimination of endogenous urates. Its rationale may be questioned when it is realized that many patients during attacks excrete urates normally or even excessively. Future work must determine how necessary purine restrictions are during attacks, but then of all times patients are receptive to instruction in those dietary restrictions which the interval treatment of gout seems to require. Complete abstinence from alcohol is advisable.

Interval Treatment of Symptomless Gout and Control of Hyperuricemia.—Gout is not cured when the attack is over. Gout is a chronic disease for which treatment must be continued indefinitely in an attempt to prevent or postpone return of symptoms. Contrary to the belief of a few physicians that no regimen materially alters the "relentless progress of gout," most physicians believe that, by adhering faithfully to the interval treatment, the majority of patients can sharply modify the course of their disease, reduce the number and severity of attacks, prevent or reduce the likelihood of chronic gouty arthritis and avoid or postpone the late and sometimes fatal renal and cardiovascular complications. The faithful and successful adherence to such a regimen, however, requires, most of all, a high degree of self-discipline on the patient's part.

13. Kersley,[21] Lockie.[34]
14. Lockie, L. M.: A Discussion of a Therapeutic Test and Provocative Test in Gouty Arthritis, Ann. Int. Med. **13**: 755-760 (Nov.) 1939.

Purine Content of Certain Foods *

List 1. Foods which contain very large amounts (150 to 1,000 mg.) of purine bodies in 100 Gm.

Sweetbreads.....	825 mg.	Kidneys (beef).....	200 mg.
Anchovies.....	363 mg.	Brains.....	195 mg.
Sardines (in oil)...	295 mg.	Meat extracts.....	160-400 mg.
Liver (calf, beef)..	233 mg.	Gravies.....	Variable

List 2. Foods which contain a large amount (75 to 150 mg.) of purine bodies in 100 Gm.

Bacon, beef, calf tongue, carp, chicken soup, codfish, duck, goose, halibut, lentils, liver sausage, meat soups, partridge, perch, pheasant, pigeon, pike, plaice, pork, quail, rabbit, sheep, shellfish, squab, trout, turkey, veal, venison

List 3. Foods which contain a moderate amount (up to 75 mg.) of purine bodies in 100 Gm.

Asparagus, bluefish, bouillon, cauliflower, chicken, crab, eel, finnan haddie, ham, herring, kidney beans, lima beans, lobster, mushrooms, mutton, navy beans, oatmeal, oysters, peas, salmon, shad, spinach, tripe, tuna fish, whitefish

Also whole grain bread and breadstuffs: graham bread, graham crackers, oatmeal crackers, rye bread, Rye Krisp, whole wheat bread, Zed

Also whole grain cereals: Bemax, bran, bran flakes, cracked wheat, Embo, graham porridge, Grapenuts, Krumbles, malt breakfast food, Pep Bran Flakes, Pettijohns, Puffed Wheat, Ralston's, Sims, Shredded Wheat, Wheaties, Wheat oats, Wheatsworth, Whole Wheat Krumbles

List 4. Foods which contain an insignificant amount of purine or no purine:

1. Beverages
   - Carbonated
   - Chocolate
   - Cocoa
   - Coffee
   - Fruit juices
   - Postum
   - Tea
2. Butter †
3. Breads and breadstuffs (except whole grain under list 3)
   - Benson's water crackers
   - Butter thins
   - Corn bread
   - Corn sticks
   - French bread
   - Gluten bread
   - Holland rusk
   - Soda crackers
   - Uneeda biscuit
   - Water rolls
   - White bread
   - Zwieback
4. Caviar
5. Cereals (except whole grain under list 3)
   - Breakfast brownies
   - Cornflakes
   - Cream of wheat
   - Farina
   - Grits
   - Post toasties
   - Puffed rice
   - Rice flakes
   - Rice krispies
   - White cornmeal
   - Yellow cornmeal
6. Miscellaneous cereal products
   - Arrowroot
   - Hominy
   - Macaroni
   - Noodles
   - Sago
   - Spaghetti
   - Tapioca
   - Vermicelli
7. Cheese of all kinds †
8. Eggs
9. Fats of all kinds (but eat in moderation)†
10. Fruits of all kinds
11. Gelatin
12. Milk
    - Buttermilk
    - Condensed milk
    - Malted milk
13. Nuts of all kinds †
    - Peanut butter †
14. Pies (except mincemeat)†
15. Shad roe
16. Sugar and sweets
17. Vegetables
    - Artichokes
    - Beets
    - Beet greens
    - Broccoli
    - Brussels sprouts
    - Cabbage
    - Carrots
    - Celery
    - Corn
    - Cucumber
    - Dandelion greens
    - Eggplant
    - Endive
    - Kohlrabi
    - Lettuce
    - Okra
    - Parsnips
    - Potato
      - Sweet
      - White
    - Pumpkin
    - Rutabagas
    - Sauerkraut
    - String beans
    - Summer squash
    - Swiss chard
    - Tomato
    - Turnips
18. Vegetable and cream soups (to be made with allowed vegetables and without meat stock)
19. Vitamin concentrates
    - Cod liver oil
    - Halibut oil
    - Yeast

* To calculate the purines or "purine bodies" in a given food the purine nitrogen is multiplied by 3: example, 200 mg. of purine nitrogen equals 600 mg. of purine bodies.
† These foods are high in fat.

Hyperuricemia and urate deposits are the result, not the cause, of gout and they bear an uncertain, perhaps even no, relationship to the acute articular attacks, but they do bear an important causal relationship to the production of chronic gouty arthritis, which represents

a foreign body reaction to the urate deposits. Hence it is necessary to combat chronic hyperuricemia (1) by dietary restrictions and (2) by the intermittent use of urate eliminants; that is, urate diuretics.

Dietary Restrictions: Each patient must be treated individually as the stage and severity of his disease and his temperament dictate. In general the diet should be free of purines on two, not necessarily consecutive, days and low in purines five days a week. Normal diets contain from 600 to 1,000 mg. of purines (that is, purine bodies) daily; a low purine diet contains from 100 to 150 mg. and can be attained roughly by allowing one food from list 2 in the accompanying table one day a week and one from list 3 four days a week, besides whatever foods are desired from list 4. Obesity should be avoided, but normal weight should be maintained. Two days each week the selections should be only from list 4 (foods free of purines). The foods in list 1 (foods rich in purines) should always be avoided entirely. It is customary to advise the avoidance also of spices, condiments and rich or indigestible foods and sauces in an attempt to prevent those gastrointestinal or particularly hepatic disturbances which may somehow initiate acute attacks. The low purine and purine-free diets just outlined may be deficient in protein, iron and vitamin B_1; generally the diet must be reinforced by administration of iron (ferrous sulfate 5 grains, or 0.3 Gm., daily) and an approved preparation of the vitamin B complex (at least 200 international units of thiamine hydrochloride and 200 Sherman-Bourquin units of riboflavin daily).

Coffee and tea are permissible, being methylated purines which do not form uric acid. Some veterans of gout insist that they can consistently tolerate certain alcoholic drinks but not others; since they cannot agree on which are harmless, the gouty novice should avoid all alcohol unless prepared to pay the price of personal experimentation.

It must be emphasized that gout may affect vegetarians and teetotalers. Purines and alcohol do not cause the disease gout any more than sugar causes diabetes. Once a person has diabetes (insulin deficiency) excessive intake of sugar may provoke symptoms. So, too, once a man has gout, and only then, will excessive intake of alcohol and purines provoke the quiescent gout into symptomatic activity and cause acute gouty arthritis (fig. 1), but so also high fat and ketogenic diets may provoke acute articular attacks.

Physicians who espouse the allergic theory consider the avoidance of purines less important than the avoidance of foods to which, regardless of their purine content, patients may be individually allergic as suggested by cutaneous tests or by their apparent provocative effect. For example, asparagus, not especially rich in purines, is said to provoke attacks in some persons. The rationale of such special restrictions is not yet clear, but physicians should cater to established idiosyncrasies.

Urate Eliminants (urate diuretics): For the many patients who cannot control symptoms and hyperuricemia by diet alone, the additional use of some urate eliminant is required: acetylsalicylic acid, sodium salicylate, sodium salicylate "augmented" by aminoacetic acid, neocinchophen or cinchophen. I believe that cinchophen is the most effective and that there is no exact substitute for it, but because of its occasional toxicity a substitute should be tried first. Salicylates augment urate excretion but generally have been considered inferior to cinchophen and ineffective except as mild analgesics unless large irritating doses are used. But Jennings[15] recently concluded that salicylates are as effective as cinchophen in controlling pain and hyperuricemia. He prescribed sodium salicylate 80 grains (5.3 Gm.) daily and sodium bicarbonate from 120 to 150 grains (8 to 10 Gm.) daily for three or four consecutive days each week to be continued indefinitely as interval therapy. Others prescribe acetylsalicylic acid from 60 to 80 grains (4 to 5.3 Gm.) daily, four consecutive days each week. Another scheme, based on Quick's report[16] that aminoacetic acid (glycine) augments the uricosuric action of salicylates is this: sodium salicylate 60 grains (4 Gm.) and aminoacetic acid 150 grains (10 Gm.) daily three consecutive days a week.

If symptoms of the disease and the hyperuricemia are not satisfactorily controlled by diets and these drugs, I believe that the intermittent use of cinchophen is justified except for those patients who have hepatic dysfunction or an idiosyncrasy to cinchophen or who are unwilling to accept the slight risk. At the Mayo Clinic we use the plan of Graham:[17] cinchophen 7½ grains (0.5 Gm.) three times daily for three consecutive days each week. The drug is continued thus indefinitely, but occasionally the dose is reduced or the drug withheld temporarily as control of gouty symptoms and of hyperuricemia permit. If the blood uric acid becomes normal or nearly so, the drug may be temporarily omitted or given for a while only one or two days a week in the usual doses or in smaller doses three days a week. Some physicians "go half way" in the matter of cinchophen and regard the use of neocinchophen from 5 to 7½ grains (0.3 to 0.5 Gm.) three times a day, two or three days every week or two, as a satisfactory compromise, but no final opinion can be given as to whether this is safer than cinchophen.

"Precautions" Against Cinchophen Toxicity: Whenever cinchophen is given, certain precautions must be taken: the ingestion of about 2 liters of fluid daily and of liberal amounts of carbohydrates. Cinchophen carries a definite risk, which some physicians never condone but which most students of gout[18] consider justifiable if gout is uncontrolled otherwise. Serious toxic reactions from cinchophen are, after all, rather rare, especially in gouty patients. The chances of serious or fatal intoxication from cinchophen in gouty patients is believed to be only a small fraction of 1 per cent. This risk must be contrasted with that of the disease itself: in from 10 to 20 or more per cent of cases gouty nephritis develops which is sometimes fatal,[19] and the incidence of renal colics from urate gravel and of cardiovascular lesions is notable. Since the disease thus carries a much greater risk than its treatment by cinchophen, it seems justifiable to assume the small risk of the latter, when necessary, to try if possible to prevent the articular, renal and vascular consequences of gout. Patients should be told of the risk of toxic reactions

15. Jennings, G. H.: The Value of Sodium Salicylate in the Treatment of Gout, in Buckley, C. W., editor: Chronic Rheumatic Diseases, London, H. K. Lewis & Co., 1937, No. 3, pp. 106-115.

16. Quick, A. J.: The Relationship Between Chemical Structure and Physiological Response: IV. Conjugation of Salicylic Acid with Glycine and Its Action on Uric Acid Excretion, J. Biol. Chem. **101:** 475-485 (July) 1933.

17. Graham, George: The Treatment of Gout: President's Address, Proc. Roy. Soc. Med. (Sect. Therap. & Pharm.) **20:** 1-10 (Jan.) 1927; Effect of Atophan on Uric Acid Excretion, Proc. Roy. Soc. Med. **20:** 257, 1926.

18. Hench, P. S.: Comments on the Diagnosis and Management of Gout in Certain Parts of the United States, Proc. Staff Meet., Mayo Clin. **12:** 262-269 (April 28) 1937.

19. Schnitker, M. A., and Richter, A. B.: Nephritis in Gout, Am. J. M. Sc. **192:** 241-252 (Aug.) 1936. Kinell, Jack, and Haden, R. L.: Gout: A Review of Sixty-Two Cases, M. Clin. North America **24:** 429-441 (March) 1940. Brøchner-Mortensen, Knud: Diagnosis of Gout, Acta med. Scandinav. **99:** 538-562, 1939. Hench, Vanzant and Nomland.[1]

from cinchophen and instructed to report such unusual symptoms as anorexia, dyspepsia, nausea, loss of weight, pruritus or jaundice, to stop taking the drug at once, and to report for special therapy (carbohydrates intravenously, high carbohydrate diet, vitamin supplements and so on).

Alkalis: During the administration of urate diuretics, patients should take enough alkali to insure constant urinary alkalinity in order to prevent renal colic from the precipitation of urate gravel or stones in acid urine. They can learn to test the urine with litmus paper to determine the amount of alkali individually required; this varies somewhat, but potassium citrate from 15 to 30 grains (1 to 2 Gm.) three times a day or sodium bicarbonate from 30 to 60 grains (2 to 4 Gm.) three times a day generally suffices. These amounts of sodium bicarbonate occasionally produce gastrointestinal disturbances which may be erroneously ascribed to cinchophen; if these occur, an alternate method of urinary alkalization is necessary.

Other Measures: Contrary to general opinion, a few physicians consider colchicine to be a preventive of acute attacks and prescribe $\frac{1}{120}$ grain (0.53 mg.) three times a day for two or three days each week or in one week of each month. With similar intent others [20] gave from 330 to 3,300 international units of vitamin B_1 (thiamine hydrochloride) daily continuously even though initial doses commonly provoked acute attacks. The value of such therapy is not established. Of more certain value is the constant avoidance of the several known provocatives of gout, not only the gastronomic but also the traumatic, medicinal, psychic, surgical and infectious provocatives. Acute postoperative gouty arthritis generally can be prevented by the use of a high carbohydrate, purine-free diet and cinchophen (or substitute) for five days before and also for five days after operation.[6] Improved control of gouty patients after removal of obviously infected foci has been reported.

There is disagreement as to the value of physical therapy (aside from simple heat or cold) during acute gouty arthritis and the intervals thereafter. Most physicians regard massage and exercises to be absolutely contraindicated at any stage of the attacks but helpful as a feature of interval therapy.[21] But "cure crises" are often precipitated by such therapy; hence I do not recommend it.

Treatment of Chronic Gouty Arthritis.—Chronic gouty arthritis may be prevented by the regimen outlined; if not, various types of physical therapy are required, especially heat to foster resorption of urates. Fever therapy or typhoid vaccine reactions have been used occasionally. Massage, exercise and spa therapy must be used cautiously lest an exacerbation be evoked.

Treatment of Tophaceous Ulcers.—Large tophi on the hands and feet may ulcerate (in later phases of gouty arthritis) and partially heal, only to break down intermittently, sometimes discharging urates for months; occasionally they become infected, necessitating consideration of amputation. This eventuality can be avoided by the early excision of tophi in which ulceration is present or impending. When débridement is done thoroughly, prompt healing occurs. Unless the tophus is small it is best, before removal, to institute the regimen for the prevention of postoperative gouty arthritis.

Treatment of Renal and Other Complications.—The treatment of gouty nephritis involves a generous intake of fluids (2 or 3 liters daily), restrictions of protein as necessary, and continued efforts to combat the underlying gout and its hyperuricemia. Prevention of gouty calculi by urinary alkalization has been mentioned already. Nonopaque to roentgen rays, such calculi are usually small and pass without surgical intervention. There is no specific treatment for the cardiovascular complications of gout.

Prognosis: Results of Treatment.—Prognosis is best for those whose symptoms develop late, poorest for those with symptoms early in life, especially in their teens. Some patients have mild gout for years, only symptomatic on rare occasions after special stress such as a surgical procedure. Despite instructions, patients may fail to control their gout because of half hearted application of the regimen (the most common reason), because their gout is uncontrollable by diet alone (the next most common reason), because of irritating occupational or other trauma, the unwitting use of some medicinal provocative, or because of the presence of some chronic aggravating infection, blood dyscrasia, such as polycythemia or leukemia, chronic plumbism or coincidental metabolic fault (unsuspected mild diabetes or thyroid dysfunction). The correction of these factors usually results in improved control of the disease. Cases of truly uncontrollable or irreversible gout are not as common as some physicians suppose.

20. Callahan, E. J., and Ingham, D. W.: Gout: Report of Nine Cases with a New Addition to the Treatment, M. Rec. **149**: 167-168 (March 1) 1939. Vorhaus and Kramer.[8] Kühnau, J.; Schroeder, H., and Wolff, O.: Einiges über die klinische Anwendung des Vitamins B_1, Deutsche med. Wchnschr. **2**: 1407-1409 (Sept. 10) 1937.

21. Kersley, G. D.: Gout, Brit. J. Rheumat. **2**: 22-26 (July) 1939.

THE CLINICAL SYNDROME ASSOCIATED WITH INTERCAPILLARY GLOMERULOSCLEROSIS

WILLIAM B. PORTER, M.D.
AND
HARRY WALKER, M.D.
RICHMOND, VA.

In 1936 Kimmelstiel and Wilson [1] reported on a group of 8 patients showing a striking hyaline thickening of the intercapillary connective tissue, most clearly seen at the hilus of the glomeruli. They felt that the change was degenerative and suggested that arteriosclerosis and diabetes mellitus played a part in its causation. The most significant clinical features of their cases were diabetes mellitus, usually of long duration, edema of the nephrotic type, gross albuminuria and varying degrees of hypertension.

This report is concerned with an analysis of the clinical and laboratory features of 8 patients who had mild diabetes mellitus, 6 of these showing at autopsy the intercapillary lesions in the glomeruli as described by Kimmelstiel and Wilson. Permission for autopsy on the other 2 was not obtained but we feel that their clinical course justifies the conclusion that they too would have shown these changes in the kidney.

REPORT OF CASES

CASE 1.—*History.*—J. W., a Negro aged 59, admitted to the medical service Oct. 27, 1937, complained chiefly of pain and tenderness of the left foot of three weeks' duration. One week previously his physician examined him and discovered

Dr. Paul Kimmelstiel analyzed the pathologic data.

From the Department of Internal Medicine, Medical College of Virginia.

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1. Kimmelstiel, Paul, and Wilson, Clifford: Intercapillary Lesions in the Glomeruli of the Kidney, Am. J. Path. **12**: 83-98 (Jan.) 1936.

glycosuria. Polydipsia had been present for at least two years, swelling of the legs for three months and impairment of vision for a year or longer. He had been a bed patient since the onset of the involvement of the left foot.

The patient was well developed and well nourished. When he was examined he was lying flat in bed; there was no dyspnea and no distress. The temperature was 103.8 F., the pulse rate 110 and the respiratory rate 22 a minute. Examination of the optic fundi showed slight blurring of the nasal side of the disk and old exudates in both fundi, with marked arteriosclerosis of the retinal arteries. The heart was apparently normal in size and shape and there were no murmurs. There was no venous stasis. The blood pressure was 160-170 systolic and 90-105 diastolic. There were signs of patchy bronchopneumonia in both lungs. There was marked generalized arteriosclerosis, and no pulse was recorded in the posterior tibial or dorsalis pedis of either lower extremity. Ischemic gangrene of the anterior third of the left foot was present. There was moderate edema in the lumbosacral area.

Laboratory examination revealed the hemoglobin content to be 80 per cent, the red blood cell count 3,750,000 and the white blood cell count 22,750-34,240 with polymorphonuclear neutrophils 85 per cent-92 per cent. Urinalysis showed: specific gravity 1.020, albumin 3 +, sugar 2 +, acetone 0, and sediment containing a few hyaline and granular casts. Blood sugar was 206-296 mg. and nonprotein nitrogen 38-44 mg. per hundred cubic centimeters; total protein 4.8 Gm., albumin 2.6 Gm. and globulin 2.2 Gm. per hundred cubic centimeters, and cholesterol 320 mg. per hundred cubic centimeters.

During his stay in the hospital the gangrene of the left foot progressed and fever, varying from 102 to 104.4 F., continued. On the seventh hospital day the left leg was amputated below the knee. The bronchopneumonia became more widespread and the patient died on the fifteenth hospital day.

Necropsy.—There were marked generalized arteriosclerosis and bilateral bronchopneumonia. The heart weighed 330 Gm. Microscopically the kidneys showed intercapillary glomerulosclerosis of moderate degree but far in excess of mere aging processes. There was only a moderate degree of diffuse arteriosclerosis and no tubular dilatation. There was considerable edema of the interstitium between the tubules, particularly in the cortex and scattered foci of polymorphonuclear leukocytes, lymphocytes and a few monocytes and plasma cells. The microscopic changes were those of acute serous interstitial nephritis and moderate intercapillary glomerulosclerosis.

CASE 2.—*History.*—J. K., a white man aged 62, seen in the outpatient department Oct. 7, 1935, complained chiefly of breathlessness with effort and recurring episodes of nocturnal dyspnea accompanied by cough.

Examination of the optic fundi revealed arteriosclerosis 2 + and no hemorrhages, exudates or edema of the disk. There was moderate cardiac hypertrophy; the second pulmonic sound was decidedly accentuated. Medium moist rales were heard at the lung bases. The blood pressure was 208 systolic and 124 diastolic; the pulse rate was 96; there was sinus rhythm. There was no dependent edema.

On laboratory examination the urine had a specific gravity of 1.025, albumin 2 + and sediment containing occasional hyaline casts. A blood count was normal and the Wassermann reaction was negative. Blood sugar was 154 mg. and nonprotein nitrogen 43 mg. per hundred cubic centimeters.

The patient was referred to the hospital for treatment and was discharged October 21. The diagnosis was hypertension, coronary insufficiency, cardiac hypertrophy, left ventricular failure and mild diabetes mellitus.

The patient was readmitted March 7, 1936, the chief complaint being breathlessness and recurring attacks of severe pain in the epigastrium radiating around the right costal margin.

The blood pressure was 230 systolic and 120 diastolic. There was tenderness over the gallbladder area, but otherwise no material change was found.

Urinalysis showed: specific gravity 1.024, albumin 2 +, sugar 0 and sediment 0. Blood sugar was 157-224 mg. and nonprotein nitrogen 43 mg. per hundred cubic centimeters.

An added diagnosis of cholelithiasis was made.

The patient was admitted for the third time on November 3 with the chief complaint of pain in the upper right quadrant of three days' duration. The diagnosis was gallstone colic.

He was admitted for the fourth and final time on Feb. 3, 1937 with the chief complaint of orthopnea and progressive edema of the lower extremities.

When examined the patient was dyspneic and was propped up in bed. The heart was greatly enlarged. The blood pressure was 170-190 systolic and 118-120 diastolic. The pulse rate was 90-110 a minute; there was sinus rhythm. General venous hypertension was present. Postural edema extended up to the umbilicus. There were bilateral pleural effusion and moderate ascites.

On laboratory examination the urine showed a specific gravity of 1.030, albumin 3 + and sugar 0 and sediment containing a few hyaline and granular casts. Blood sugar was 162 mg., nonprotein nitrogen 55 mg. per hundred cubic centimeters; total protein 4.4 Gm., albumin 2.1 Gm. and globulin 2.3 Gm. per hundred cubic centimeters, and cholesterol 152 mg. per hundred cubic centimeters.

The patient became progressively worse and died on the tenth hospital day.

Necropsy.—The condition shown at necropsy was generalized arteriosclerosis; pronounced coronary sclerosis, cardiac hypertrophy (weight 700 Gm.); chronic passive congestion and cardiac cirrhosis of the liver. Microscopically the kidneys showed severe arteriosclerosis and arteriolar sclerosis and intercapillary glomerulosclerosis of a moderate degree. The tubules showed vicarious hyperplasia and hypertrophy.

CASE 3.—*History.*—M. T., a white woman aged 41, was admitted to the surgical service April 25, 1937 and died April 26. Her chief complaint was pain in the right lower quadrant, which was followed by generalized abdominal pain and tenderness. The illness was of thirty-two hours' duration. There was a history of polyuria and polydipsia for "many years," but no diagnosis of diabetes had been made.

On examination the patient was extremely ill. The temperature was 103.4 F., the pulse rate 120-140 and the respiratory rate 25-30 a minute. The heart and lungs were essentially normal; the arteries showed moderate arteriosclerosis. The blood pressure was 100-120 systolic and 65-75 diastolic. The phenomena of generalized peritonitis were evident.

Urinalysis showed a specific gravity of 1.032, albumin 4 +, sugar 2 + and sediment 0. A blood count showed hemoglobin 100 per cent, red cells 5,200,000 and white cells 7,350, with a differential of 92 per cent polymorphonuclear neutrophils. The blood sugar was 400 mg. and nonprotein nitrogen 54 mg. per hundred cubic centimeters.

The patient died fourteen hours after admission to the hospital.

Necropsy.—This revealed generalized fibropurulent peritonitis following a ruptured gangrenous appendix. The heart weighed 350 Gm. The kidneys showed a moderate degree of intercapillary sclerosis involving all the glomeruli. The medium sized arteries showed only a slight degree of sclerosis, but there was a severe and diffuse arteriolar sclerosis. The tubules showed acute dilatation and there was some interstitial serous nephritis.

CASE 4.—*History.*—E. Mc., a Negro woman aged 55, was admitted to the medical service on Sept. 23, 1936 and died October 21. Her chief complaint was diarrhea with swelling of the feet, legs and abdomen. The swelling began in her feet in March 1936. This progressively increased until it became generalized, including the face. Diarrhea began three weeks before her admission to the hospital. The only significant statements suggesting diabetes were an excessive appetite with loss of weight, polyuria and polydipsia. Ten years previously, at a time when she felt well, she had expectorated blood on one occasion. There had been intermittent vaginal bleeding for three years and bleeding hemorrhoids for ten or more years.

Physical examination revealed generalized edema including the face, ascites and bilateral pleural effusion. The heart was normal. The blood pressure was 160-180 systolic and 80-90 diastolic. The peripheral vessels showed arteriosclerosis and atherosclerosis; the venous pressure was normal. The optic fundi showed arteriosclerosis 1 + and no edema, hemorrhages or exudates.

Urinalysis showed: specific gravity 1.016-1.018, albumin 3 + - 4 +, sugar 0, and sediment containing occasional hyaline and granular casts. A blood count showed hemoglobin content 48 per cent, red cells 2,520,000, and white cells 5,600 with a normal differential count. The hematologist who was consulted stated that the picture presented by the blood studies was that of chronic blood loss. The blood sugar was 196-260 mg., nonprotein nitrogen 30-53 mg., and cholesterol 224 mg. per hundred cubic centimeters; total protein 4.9 Gm., albumin 2.1 Gm. and globulin 2.8 Gm. per hundred cubic centimeters.

Necropsy.—The heart weighed 250 Gm. Submucous uterine fibroids were present. Microscopically the kidneys showed severe and diffuse arteriosclerosis and arteriolar sclerosis. The glomeruli showed advanced intercapillary sclerosis with occasional degenerative glomerulitis and numerous adhesions with extensive changes in the capsules. The tubules showed severe tubular dilatation and extensive metallaxis.

CASE 5.—*History.*—H. C., a white man aged 57, was admitted to the medical service on Sept. 12, 1936 and died September 13. He was admitted because of unconsciousness which developed suddenly and had become increasingly more complete. A history of diabetes "for many years" was obtained from the family.

When examined the patient was completely unconscious, and there was a flaccid paralysis of the left arm and leg. The optic fundi showed arteriosclerosis 2 + of the retinal vessels and many fresh hemorrhages, but there was no exudate or edema of the disk. The heart was moderately enlarged to the left, with a rate of 102. The peripheral arteries showed a moderate degree of arteriosclerosis. The blood pressure was 200 systolic and 104 diastolic. There was pitting edema of the legs extending to the thighs.

Urinalysis showed: specific gravity 1.025, albumin 4 +, sugar 1 +, sediment 0. The blood sugar was 320 mg., nonprotein nitrogen 46 mg. per hundred cubic centimeters; total protein 4.6 Gm., albumin 2.2 Gm. and globulin 2.4 Gm. per hundred cubic centimeters.

Death occurred a few hours after admission to the hospital, probably the result of a cerebral hemorrhage.

Necropsy.—This was confined to the left kidney. There was advanced intercapillary glomerulosclerosis with obvious deposition of hyaline and fat in the parietal capsule. There was extensive sclerosis of the arteries and arterioles. The tubules showed vicarious hyperplasia and hypertrophy. There were extensive metallaxis and scarring of the kidney tissue.

CASE 6.—*History.*—H. S., a Negro aged 52, admitted to the medical service July 31, 1939 and discharged August 17, complained chiefly of swelling of the legs and abdomen of three months' duration and mild breathlessness with effort. The patient stated that sugar had been found in his urine three years previously but that he had not followed the treatment prescribed.

The patient was moderately dyspneic, with extensive edema of the legs and sacral area, together with a moderate amount of ascites and bilateral pleural effusions. The optic fundi showed a moderate degree of sclerosis of the retinal vessels but no exudates or hemorrhage. The heart was enlarged, with a cardiothoracic ratio of 57 per cent. An electrocardiogram showed T_1 and T_2 isoelectric, with left axis deviation. The blood pressure was 175-185 systolic and 100-110 diastolic, pulse rate 88-96 a minute. There was moderate venous hypertension. The liver was 4 cm. below the costal margin; ascites was moderate.

Urinalysis showed: specific gravity 1.020-1.022, albumin 3 +, sugar 0-1 +, sediment 0. A blood count showed hemoglobin content 84 per cent, red cells 4,200,000; the leukocyte and differential counts were normal. The blood sugar was 192-246 mg., nonprotein nitrogen 36 mg., cholesterol 214 mg., and total protein 4.3 Gm., albumin 2.1 Gm. and globulin 2.2 Gm. per hundred cubic centimeters.

The clinical diagnosis was (1) cardiac hypertrophy and dilatation, (2) coronary insufficiency, (3) generalized arteriosclerosis, (4) mild congestive heart failure, (5) mild diabetes mellitus and (6) intercapillary glomerulosclerosis.

The patient showed satisfactory improvement after institution of a salt-poor diabetic diet, bed rest and mercury diuretics. He was discharged to the cardiac and diabetic clinics.

He was readmitted September 23. During his second hospital admission generalized edema, ascites and recurring pleural effusions were the most prominent clinical symptoms. Heart failure of the congestive type was never conspicuous, yet it existed to a mild degree. The blood pressure ranged from 140-160 systolic and 90-110 diastolic.

Urinalysis showed: specific gravity 1.012-1.018, albumin 4 +, sugar 0-1 +, sediment 0. Blood counts showed: hemoglobin content 80-85 per cent, red cells 4,100,000-4,300,000, with normal leukocyte and differential counts. The blood sugar was 150-220 mg., nonprotein nitrogen 34-48 mg., cholesterol 270-296 mg. per hundred cubic centimeters; total protein 4.5-5.1 Gm., albumin 2.2-2.5 Gm. and globulin 2.3-2.6 Gm. per hundred cubic centimeters.

The hospital course was characterized by unsustained improvement following administration of digitalis and diuretics, frequent thoracentesis and controlled diet. Death resulted from bronchopneumonia on December 9.

Necropsy.—The heart weighed 500 Gm. There was severe coronary arteriosclerosis. The lungs showed bronchopneumonia, bilateral, involving the lower lobes. Microscopically the kidney showed severe arteriosclerosis, arteriolar sclerosis and extensive intercapillary sclerosis involving practically all of the glomeruli. There was vicarious hyperplasia and hypertrophy with deposition of fat and some hyaline droplets, degeneration of the tubules and a moderate degree of metallaxis.

Basement membrane stain. Thickened and hyalinized intercapillary connective tissue more pronounced, though of the same type as seen in the aging process of glomerulus. The capillary loops, endothelial and epithelial cells are normal. (Case of diabetes in middle aged person.)

CASE 7.—A. C., a white woman aged 67, admitted to the outpatient department in January 1935, complained chiefly of loss of 50 ± pounds (23 Kg.), breathlessness with effort, moderate edema of the ankles and polyuria. Examination revealed hypertension; the blood pressure was 210 systolic and 120 diastolic; there were general arteriosclerosis and probably cardiac enlargement but no phenomena of heart failure. Urinalysis showed albumin 2 + and sugar 3 +. The blood sugar was 280 mg. per hundred cubic centimeters. She was followed as an ambulatory patient in the diabetes clinic until Dec. 4, 1936.

She was first admitted to the hospital in the medical service on Jan. 5, 1938, and from this date until she left the city in December 1939 she was admitted eight times, remaining in the hospital on an average of eleven days.

The chief complaints on each admission were essentially the same, yet there was some variability in their severity. Breathlessness with effort was consistently present, but with

each admission edema was a prominent complaint, and on four occasions the edema was extensive and complicated by hydrothorax and ascites. The optic fundi showed arteriosclerosis 1 +, without exudates or hemorrhages. The heart was moderately enlarged with a cardiothoracic ratio of 54 per cent. An electrocardiogram showed left axis deviation and moderately inverted T_1. The blood pressure was 165-190 systolic and 95-110 diastolic. The venous pressure was 110-120 mm. of water.

Urinalysis showed specific gravity 1.014-1.022, albumin 2 +-4 +, sugar 0-2 +, sediment 0. Blood counts showed: hemoglobin content 75-85 per cent, red cells 3,400,000-4,100,000 and white cells 7,800-9,600, with a normal differential count. The blood sugar was 140-310 mg., nonprotein nitrogen 27-48 mg., and cholesterol 186-264 mg. per hundred cubic centimeters and total protein 4.4-5.1 Gm., albumin 2.4-2.6 Gm. and globulin 1.7-2.6 Gm. per hundred cubic centimeters.

TABLE 1.—*Symptoms and Signs of the Syndrome of Intercapillary Glomerulosclerosis*

Condition	Per Cent
Diabetes mellitus	100
Albuminuria, 2-4+	100
Hypertension, under 200	63.3
Hypertension, over 200	36.6
Hypoalbuminemia, 2-6%	100
Edema, significant	75
Anemia, hemoglobin 80%+	87.5
Anemia,* hemoglobin 48%	12.5
Nonprotein nitrogen, less than 50 mg. per 100 cc.	50
Nonprotein nitrogen, 50 to 65 mg. per 100 cc.	50
Retinal changes,† arteriosclerosis	100
Retinal hemorrhage and exudates	50

* Associated with chronic hemorrhage.
† Two cases not examined.

The patient was consistently partially relieved of the edema by mercury diuretics in conjunction with ammonium chloride. The diabetes was moderately controlled with diet. The impression at the time of the last hospital admission was that her life expectancy was short and that death would result from cardiac and renal failure.

The clinical diagnosis was (1) hypertension, arteriosclerosis, cardiac hypertrophy, myocardial fibrosis, coronary artery sclerosis; (2) diabetes mellitus, mild; (3) nephrosclerosis with intercapillary glomerulosclerosis, severe; (4) nephrotic syndrome; (5) heart failure, congestive type, mild.

CASE 8.—C. W., a white woman aged 39 at the time of her death on Feb. 1, 1938, was first admitted to the medical service April 4, 1929 with a diagnosis of pyogenic infection of the right thumb and diabetes. The blood pressure was 100 systolic and 68 diastolic. Urinalysis showed specific gravity 1.022, albumin 0, sugar 3 +. The nonprotein nitrogen was 26 mg. and the blood sugar 344 mg. per hundred cubic centimeters.

From 1929 to 1932 she was readmitted for various types of cutaneous infection, but nothing specific was noted, the diabetic state being partially controlled with diet and insulin.

She was readmitted to the hospital on April 14, 1932 because of pains in the lower extremities and edema of the ankles and eyelids. Examination showed edema of the eyelids, normal fundi, subnormal blood pressure, 98 systolic and 65 diastolic, slight edema of the ankles with absence of pulsation in the posterior tibial and dorsalis pedis arteries, diminished deep reflexes of the knee and achilles tendon.

The electrocardiogram was normal. The basal metabolic rate was +2 per cent. Urinalysis showed specific gravity 1.026, albumin 2 +, sugar 3 +, sediment 0. The blood count was normal. The blood sugar was 148-344 mg., nonprotein nitrogen 27-42 mg., cholesterol 276 mg. per hundred cubic centimeters; total protein 5 Gm., albumin 3.3 Gm., globulin 1.7 Gm. per hundred cubic centimeters. She was discharged to the diabetic clinic for treatment after eleven days of hospital care.

She was readmitted to the hospital on May 13, 1937 because of progressively increasing edema of the legs and abdomen, weakness, pain in the feet and slight breathlessness with effort, which developed after the edema extended to the abdomen. Physical examination showed edema of the lower extremities with a moderate amount of ascitic fluid, a blood pressure of 160 systolic and 80 diastolic, and generalized arteriosclerosis with absence of pulsation in the posterior tibial and dorsalis pedis arteries. The optic fundi showed arteriosclerosis of the retinal vessels 1 + and an occasional flame hemorrhage; there was no edema of the disk.

Urinalysis showed specific gravity 1.016, albumin 3 +, sugar 0 and sediment 0. The hemoglobin content was 78 per cent and red blood cells numbered 3,740,000. Blood sugar was 137-220 mg., nonprotein nitrogen 35-38 mg. and cholesterol 412 mg. per hundred cubic centimeters. The patient showed some improvement on a diabetic regimen with insulin, bed rest and mercury diuretics. She was discharged to the diabetes clinic.

She was readmitted on October 16 because of generalized edema and breathlessness. Physical examination showed generalized extensive edema, ascites and pleural effusion on the right side. The optic fundi showed no edema of the nerve head; there were superficial and deep hemorrhages and many cotton wool exudates; arteriosclerosis was 2 +. There was generalized arteriosclerosis. A teleroentgenogram revealed a cardiothoracic ratio of 51 per cent; the blood pressure was 170 systolic and 100 diastolic. The electrocardiogram was normal. There were no evident signs of congestive heart failure.

Urinalysis showed specific gravity 1.011-1.020, albumin 4 +, sugar 0-1 + and sediment 0. A blood count showed hemoglobin content 70 per cent, red cells 3,620,000 and white cells 7,400, with a normal differential count. Blood sugar was 150-186 mg., nonprotein nitrogen 40-52 mg. and cholesterol 160-204 mg. per hundred cubic centimeters and total proteins 4.2-4.4 Gm., albumin 2.6-2.8 Gm. and globulin 1.6-1.8 Gm. per hundred cubic centimeters. The congo red test showed retention of 66 per cent of the dye for sixty minutes. The phenolsulfonphthalein test resulted in 24 per cent excretion for two hours.

There was a moderate reduction in the edema following the use of mercury diuretics and the restriction of salt and water. The right pleural cavity was aspirated three times; the total fluid removed was 2,650 cc., which had a specific gravity of 1.012-1.014. The patient was discharged from the hospital on Jan. 29, 1938 and died at her home February 1.

There was no autopsy. The clinical diagnosis was (1) diabetes mellitus, (2) generalized arteriosclerosis, (3) severe intercapillary glomerulosclerosis, (4) nephrotic syndrome and (5) renal insufficiency (table 1).

COMMENT

In the choice of cases for this study we have selected patients who showed both advanced and mild degrees of hyaline thickening of the intercapillary tissue of the glomeruli. Also included are two patients who were followed clinically from an early stage to the time the syndrome became fully developed. An analysis of these cases shows that the well developed syndrome probably represents the end stage of a progressive process, the latter phase being preceded by certain suggestive clinical changes and laboratory studies, one of these being the appearance of albuminuria during the course of mild diabetes in a patient past the fourth decade. A review of case 8 illustrates the most probable course of events and its relation to the progress of the renal lesions. The diagnosis of diabetes mellitus was made in 1929. Albuminuria, mild edema, arteriosclerosis and

TABLE 2.—*Heart Weights*

Case	Heart Weight in Gm.	Sex	Age	Blood Pressure		Cardiothoracic Ratio, per Cent
				Systolic	Diastolic	
1. J. W.	330	♂	59	160-170	90-105	
2. J. K.	700	♂	62	170-208	90-124	
3. M. T.	350	♀	41	*100-120	65- 75	
4. E. Mc.	250	♀	55	160-180	80- 90	
5. H. C.	No data	♂	57	200	100	
6. H. S.	500	♂	52	140-185	90-110	
			No Autopsy			
7. A. C.	...	♂	67	210	120	54
8. C. W.	...	♀	39	100-170	60-100	51

* Blood pressure probably depressed by the toxemia of peritonitis.

mild hypoproteinemia were first recognized three years later in 1932. At this time the blood pressure was 98 systolic and 65 diastolic. Five years later, in 1937, the edema was excessive, the blood pressure 160 systolic and 80 diastolic, arteriosclerosis more advanced, albuminuria 3+ and total proteins of 4.1 Gm. per hundred cubic centimeters. The patient died in 1938 after a prolonged illness characterized by generalized edema of the nephrotic type, and hypertension (160-180 systolic and 80-95 diastolic). The immediate cause of death is not known, for the patient died at home; however, renal insufficiency was evident when the patient left the hospital.

In this series of cases, both from the clinical standpoint and from the autopsy material studied, one is impressed not only by the renal lesions but also by the arteriosclerosis throughout the vascular tree, particularly in the coronary, mesentery and the arteries of the lower extremities. Hypertension was found at some time during the period of observation in all except case 3; yet in only three cases did the pressure exceed 200 mm. of mercury systolic at any time during observation. The heart weights (table 2) were in three instances within the range of normal from 250 to 350 Gm., and in case 8 there was no significant cardiac enlargement. These facts suggest that the associated hypertension was of a mild type or of short duration.

Newburger and Peters [2] in a recent report state that the pathogenesis of this condition may "depend on severe and extensive arterial and arteriolar degeneration associated with and perhaps resulting in diabetes mellitus, hypertension and renal damage." They also emphasize the fact that the cases studied by them presented many of the features of malignant hypertension. This may be true at times, but from a study of our material we cannot conclude that features of malignant hypertension are an essential aspect of the clinical syndrome of intercapillary glomerulosclerosis. In fact, none of our patients, with the possible exception of the first one, showed the presence of the optic fundus changes characteristic of malignant hypertension, nor did the kidneys in any case show the arteriolar changes characteristic of malignant nephrosclerosis. With regard to the relationship of diabetes mellitus to renal lesions and hypertension, it may be safely stated that from a study of our cases it is evident that diabetes mellitus either preceded or developed concomitantly with the intercapillary glomerulosclerosis. In one case diabetes mellitus existed for many years and was complicated by albuminuria, hypoproteinemia and edema before hypertension developed. This suggests that the changes in the glomeruli and renal vascular apparatus did not result from but preceded the hypertension. In contrast to the diabetes mellitus, the hypertension appears at a later stage, corresponding to the time when the renal vascular lesions have become advanced.

In 1935 Kimmelstiel [3] described in the arteriosclerotic kidney a broadening and hyalinization of the intercapillary axial connective tissue. He interpreted the changes as an aging phenomenon of the glomerulus. It would appear that the changes observed in the patients under consideration represent an accelerated and advanced aging phenomenon, probably related to or possibly precipitated by diabetes mellitus. It has been recognized for some time that patients who have mild diabetes mellitus and who have reached the fourth decade do have accelerated vascular changes in the coronary and peripheral arteries, and often with only mild degrees of hypertension; frequently the vascular changes are more pronounced in one area of the vascular tree than in another—the reason for which is not clear. Therefore it is suggested that the intercapillary changes in this group of patients may represent another instance of a predilective degenerative process occurring in mild diabetes mellitus which culminates in the syndrome under discussion.

2. Newburger, R. A., and Peters, J. P.: Intercapillary Glomerulosclerosis; A Syndrome of Diabetes, Hypertension and Albuminuria, Arch. Int. Med. **64**: 1252-1264 (Dec.) 1939.

3. Kimmelstiel, Paul: Glomerular Changes in Arteriosclerotic Contraction of the Kidney, Am. J. Path. **11**: 483-496 (May) 1935.

CONCLUSIONS

1. Intercapillary glomerulosclerosis is an accelerated aging process occurring in mild diabetes mellitus and is accompanied by widespread arteriosclerosis.

2. The well developed syndrome is characterized by mild diabetes mellitus, albuminuria, varying degrees of hypertension, arteriosclerosis, edema and hypoproteinemia. The development of the renal changes alters the clinical course of an otherwise mild diabetes mellitus leading to a serious and progressive malady.

1201 East Broad Street.

ABSTRACT OF DISCUSSION

DR. SOMA WEISS, Boston: Intercapillary glomerulosclerosis is primarily a descriptive term indicating a certain type of focal lesion of the renal glomerulus. Frequently, it is but an accidental microscopic finding without clinical significance. Glomerulosclerosis represents a degenerative process occurring usually in association with renal arteriosclerosis or arteriolosclerosis with or without diabetes. It can be superimposed also on the usual lesions of glomerulonephritis. Intercapillary glomerulosclerosis assumes clinical interest only if the lesions described by Drs. Walker and Porter are prominent and diffuse. Such diffuse intercapillary glomerulosclerosis is prone to be associated with albuminuria, hypoproteinemia and a tendency to anasarca. This nephrotic syndrome of intercapillary glomerulosclerosis, in contrast to that of so-called lipoid nephrosis, occurs most frequently after the age of 40 and is often associated with some degree of hypertension. Hypertension, however, is not always present. Thus, it is known that broadening of the glomerular intercapillary connective tissue, a manifestation of an aging process, can be independent of arterial hypertension. Hypertension and the renal arteriolar lesions are independent of the specific lesions of intercapillary glomerulosclerosis, although they may all depend on a common primary cause. The combination of diabetes, nephrotic syndrome and vascular sclerosis makes the diagnosis of intercapillary glomerulosclerosis probable. In recent years, such correct diagnosis has been made on several occasions in the clinic. It is significant that here we are dealing with a type of nephrotic syndrome in which the causative lesion can be clearly placed within the glomerulus. The tubules are normal or contain some fat. The clinical syndrome of nephrosis is related to various types of renal disease in which the determining lesion is probably located in the glomerulus and not in the tubules. Thus, glomerulonephritis, amyloid renal disease, glomerulonephrosis of toxemia of pregnancy, lipoid nephrosis (although glomerular lesions of etiologic significance are denied by some) and intercapillary glomerulosclerosis are associated with glomerular lesions and the nephrotic syndrome. According to this concept, we should differentiate different types of nephrosis or nephrotic syndromes.

DR. PAUL KIMMELSTIEL, Richmond, Va.: I should like to speak about the differentiation of this lesion to one which, histologically and partially clinically, may be very similar to the intercapillary glomerulosclerosis, namely a certain type of subacute glomerulonephritis which Fahr and Volhard referred to as intracapillary glomerulonephritis. I had difficulty in distinguishing these conditions from each other during the first cases. The difference I was finally able to demonstrate is shown in lantern slides. The first one is from a case of intracapillary glomerulonephritis, a subacute phase, which clinically invariably is associated with a marked degree of nephrotic syndrome.

There is a thickening of intercapillary connective tissue, just as in the intercapillary glomerulosclerosis, but the next slide shows the essential difference; namely, the peripheral capillaries are narrow and the basement membrane at the very periphery is split up. This process is one which does not spread from the hilus of the glomerulus as it does in glomerulosclerosis but is one which simultaneously involves all capillaries of the glomeruli, and therefore the peripheral capillaries as well as those in the center. In the next slide (high power) the peripheral capillary is shown to be split up and it is blurred, in contrast to the intercapillary sclerosis shown in the next two slides, in which the peripheral capillary appears as a fine line, which is not teased up and not blurred, the capillary being open rather than narrow. Although those conditions histologically as well as clinically are similar in many cases, they can easily be distinguished clinically as well as microscopically. I have observed about 12 cases of this disease in Richmond during five years, that, is within about fifteen to eighteen hundred autopsies. In my first investigation in Boston I saw 9 cases from autopsy material taken from the complete collection of the Mallory Institute from 1898 to 1934; I would say about ten times more autopsies. The seeming increase of frequency is easily explained. The cases selected in Boston were taken only from autopsies in which cardiac hypertrophy and arterial hypertension were noted during life and at autopsy. There were only 9 cases. The cases in Richmond, however, were selected consecutively throughout the entire time, and only about half of these cases really did show hypertension. Therefore I certainly agree with the authors' conception that hypertension is not an essential part of this disease and certainly does not cause it.

DR. SHEPPARD SIEGAL, New York: At Mount Sinai Hospital in New York we had been interested primarily in a clinical syndrome, and we then discovered that it was associated with the type of lesion presented here by Drs. Porter and Walker. In other words, we found that among diabetic patients there was an unusual incidence of the nephrotic picture. On study of these cases, of which it was possible to collect about 13, 5 of them which I was able to follow to necropsy all showed the typical kidney lesion just described. At present further study of this problem is being pursued from the postmortem point of view. Dr. Allen in the pathology department and I have studied 200 control cases, in none of which was diabetes present, 100 without hypertension, 100 with hypertension, and in none of the 200 cases was the lesion found at all. On the other hand, of 100 unselected diabetic patients whose kidneys were thoroughly studied, we found that 33 of them showed this lesion. They did not all show the lesion to the extent to which it has been present in the cases shown here; in some of them the lesion occurred in only a few glomeruli. Those cases in which the lesion was not extensive showed no element or no significant element of the syndrome as here presented. It is important to emphasize that the lesion may occur in diabetic patients without the syndrome. It seems to be correlated more with the diabetes than with either the hypertension or any of the other elements of the syndrome. But when the lesions are extensive it is true that then one is likely to have pretty much the fully developed syndrome which has been presented here.

DR. WILLIAM B. PORTER, Richmond, Va.: We are conscious of the fact that one is stepping on dangerous ground when one attempts to establish a clearcut syndrome when the disease is a chronic degenerative one. However, we feel that this clinical entity is fairly well established and can be recognized at the bedside, and one can anticipate that the pathologist will find what has been described by Dr. Kimmelstiel. There is one hitch in the differential diagnosis which has not been touched on, namely the differential diagnosis between subacute glomerulonephritis complicated by the nephrotic syndrome. That is a pitfall which is likely to creep into the differential diagnosis. We feel that there are two important features which should favor nephritis versus the syndrome of intercapillary glomerulosclerosis. Anemia is almost a universal finding in glomerulonephritis, whereas in intercapillary glomerulosclerosis anemia is not an important feature of the syndrome. The second and important point is that as a rule the nephrotic stage of glomerulonephritis is a disease which occurs in the age group under 50, whereas the majority of these patients are beyond 50.

TREATMENT OF UTERINE FIBROMYOMAS

WILLIAM E. COSTOLOW, M.D.
LOS ANGELES

Several years ago a report [1] was published on 604 patients with uterine fibromyoma treated between 1921 and 1926 by means of radiation therapy in our practice (Soiland, Costolow and Meland). Since that time 1,137 additional patients have been treated. A statistical analysis has been made of 1,009 of those treated between 1927 and 1937, with a follow-up of from two and one-half to twelve and one-half years. Of this group, 23 were either "lost" or impossible to follow for a two and one-half year period. However, several of these patients showed improvement when last examined, and we believe the final results would conform to the findings of the large group. It is doubtful if many of them were later operated on, as it is logical to assume that those patients who found treatment unsatisfactory would have returned. At any rate, in analyzing a large group of 986 cases, 23 missing is too insignificant greatly to affect the total average result. We have excluded patients with benign uterine bleeding and fibrosis uteri and those without uterine enlargement or nodular involvement. The size of the uterine masses in this series varied from small nodular uteri two times normal size to uterine masses the size of an eight months pregnancy.

The majority of our patients were referred by other physicians for radiation therapy. Hence most of the cases were selected especially for irradiation. One of the leading surgeons in our community has alone sent us over 200 patients whom he selected for radiation therapy instead of operation. During these years we saw, in addition, 204 patients to whom treatment was not given either because of some contraindication to radiation therapy or the patient's choice of surgical intervention. We believe the careful selection of cases is the most important single factor contributing to success in the treatment of fibroids by radiation therapy. The diagnosis of fibroid tumors should be established as definitely as possible before radiation therapy is commenced. With large tumors, this is often difficult, and we believe a good rule to follow is that in cases where doubt exists as to diagnosis, operation is the treatment of choice. We accepted a number of patients with the larger tumors, in the treatment of which radiation would usually be contraindicated, either because the patient refused to have an operation or a physical condition precluded surgical intervention. In many of these patients we have obtained surprisingly good results.

Radiation has been used successfully for many years in the treatment of certain uterine fibromyomas, and the gynecologic literature from all parts of the world is replete with reports on its success as a method of treatment in this condition. On the other hand, surgical intervention has also proved to be a satisfactory means of treatment, even though it carries a low but definite morbidity and mortality rate. A number of patients no doubt require operation; nevertheless many may be treated by radiation therapy with less morbidity and mortality.

From the Los Angeles Tumor Institute, 1407 South Hope Street.
Read before the Section on Radiology at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.
1. Soiland, A.; Costolow, W. E., and Meland, O. N.: California & West. Med. **30**: 234 (April) 1929.

Taylor [2] stated that "there should be no quarrel between the surgeon and the radiologist over the treatment of fibroid tumors—indications will become more clearly defined." Contraindications to irradiation have been established for many years and handed down through the literature. Some of these are definite and can be easily followed. Others, however, possibly are too rigid to be exactly substantiated, and patients for radiation therapy are no doubt being selected too conservatively.

Some of the factors which have been employed in the choice of a method for treating fibroid tumors are age of the patient, size and type of tumor, presence of associated pelvic disorders and effect of menopausal symptoms on the patient. It is our purpose to consider these factors in this report, together with any after-effects on the remaining uterus or residual fibroid masses in regard to later bleeding and pressure symptoms, or the subsequent development of disease.

AGE OF PATIENT

Of considerable importance in deciding between radiation therapy and surgical intervention is the age of the patient. In younger women it is, of course, desirable to attempt to preserve not only ovarian function as much as possible but in some cases also to preserve the child-bearing function. Myomectomy often achieves the desired result. The observation of Bland Sutton made many years ago that "after enucleation of a fibroid in the procreative period of life, a woman is more likely to grow another fibroid than to conceive successfully" is not exactly in keeping with more recent surgical reports. Bonney [3] reported that in a series of six hundred myomectomies for fibroid tumors only 10 patients had recurrences, and in 137 married women a total of 52 (38 per cent) became pregnant. Counseller [4] of the Mayo Clinic stated that according to statistics 35 per cent of the patients do become pregnant following myomectomy. Recurrences of myomas took place in 20 per cent of the patients younger than 40 and in 8 per cent of those more than 40 years of age.

Fortunately, the majority of uterine fibroid tumors occurs in women around 40, or near the menopausal age, when the preservation of ovarian function is unimportant. In a former series [1] the average age was 43.2, and in this series (1927 to 1937) 42.5 years, with only 26.7 per cent under 40 and 73.3 per cent over 40 years.

Hence consideration of menopausal symptoms was not so important in our series inasmuch as 73 per cent of these patients were in the menopausal age. Fibroid tumors probably occur fairly often in women in their earlier years, but in the majority of cases symptoms necessitating treatment do not arise until around the menopausal age.

ASSOCIATED PELVIC INFLAMMATION

For many years a history of previous pelvic inflammation has been mentioned in the literature as a contraindication to radiation treatment of uterine fibromyomas, but little proof has been shown of any acute infections occurring after irradiation. The fact that preexisting adnexal inflammation is present in fibromyoma has been established beyond doubt. In 150 consecutive patients with fibromyoma operated on at St. Luke's Hospital, Wood [5] found chronic adnexal infections in only 28 per cent. Other reports (Ford [6]) have shown evidence of as high as 40 per cent associated chronic inflammation in patients.

Theoretically, dilation and curettage with insertion of radium might stir up preexisting chronic inflammation. There is, however, no reason why external roentgen ray therapy should do this. In fact, this method of therapy has been successfully used in the treatment of chronic pelvic inflammation. In our series of 986 cases, in only 1 did there develop an acute inflammatory process after irradiation. The inflammation in this patient followed curettement and the insertion of radium. No acute inflammation resulted in any patient treated externally by means of roentgen rays alone. Inasmuch as 61.5 per cent of our patients were treated by radium given intrauterinely plus roentgen rays, and 5.5 per cent by radium alone, the importance of associated pelvic inflammation as a contraindication is difficult to understand.

TECHNIC

In our series, 61.5 per cent of the patients were treated by both radium and roentgen rays; 33.0 per cent, by roentgen rays alone, and only 5.5 per cent, by radium alone. In the use of both roentgen rays and radium, only small doses of each are necessary. Curettement to rule out malignant disorders as well as to discover the presence of submucous fibroid growths is important. This should be a routine procedure in practically all cases of uterine fibromyoma. If curettement is done, the application of radium at the same time is simple. In patients with severe hemorrhage, radium combined with roentgen rays will often produce a more rapid cessation of bleeding than roentgen rays alone. Usually the large tumors are better treated with roentgen rays alone. In these, because of the intervening distance, radium inserted intrauterinely may not be suitable for applying a sufficient dose to the ovaries. The amount of radium applied intrauterinely is small, approximately 1,000 to 1,200 milligram hours. An applicator with two 25 mg. radium tubes in tandem and a filtration equivalent to 1 mm. of platinum is used. This prevents strong reactions on the endometrium which might produce atresia of the canal or later leukorrheal discharge. The roentgen dose averages from 400 to 500 roentgens in the midpelvis. Increased doses were used occasionally in the large tumors. However, it is doubtful if much additional shrinkage was obtained in them from the greater amount of irradiation action on the tumor cells themselves. The cells in this type of tumor when located in other parts of the body are resistant to irradiation, and the same principle probably applies here. Some questionable evidence exists to show that even after menopause irradiation shrinkage may be induced in large tumors. A case in point in our series is as follows:

A woman aged 50 with a chief complaint of uterine tumor the size of a 4 months pregnancy applied for treatment in July 1933. She had ceased to menstruate three years previously and had had hot flashes and evidences of menopause. For the past two weeks she had noticed slight spotting of blood and pressure symptoms. Curettement was negative for malignant growths and radiation treatment was instituted. A recent examination of this patient, six and one-half years later, revealed the uterus to be atrophic.

However, most shrinkage is undoubtedly produced by the action of the rays on the ovaries with the production of the menopause.

2. Taylor, H. C., Jr.: Bull. New York Acad. Med. **11**: 368 (June) 1935.
3. Bonney, Victor: Practitioner **138**: 1 (Jan.) 1937.
4. Counseller, V. S.: Proc. Staff Meet., Mayo Clin. **14**: 817 (Dec. 27) 1939.
5. Wood, F. C.: Roentgen Treatment of Uterine Fibromyomas, J. A. M. A. **94**: 601 (March 1) 1930.
6. Ford, F. A.: Surg., Gynec. & Obst. **42**: 245 (Feb.) 1926.

EFFECT OF IRRADIATION ON MENOPAUSAL SYMPTOMS

It is difficult to determine the severity of the menopause, whether normal or artificial. As pointed out by Norris and Behney,[7] the severity depends on the age of the patient, the temperament, the nervous stability and many other conditions. Burnam,[8] in a review of 1,800 patients with irradiation menopause, concluded that "artificial menopause is not a serious thing from either the physical or the psychic standpoint." He also pointed out that 50 per cent of all patients on whom hysterectomy has been performed with preservation of the ovaries have early menopause—in any event, within four years of operation. Norris and Behney[7] reported that 89.7 per cent of their patients with irradiation menopause were able to carry on with their usual duties and 15.8 per cent had no menopausal symptoms.

Women differ widely in regard to the importance of ovarian function. In our series, 15 per cent had no flashes or nervous symptoms whatsoever and only 10 per cent later required sedatives or endocrine therapy because of really severe menopausal symptoms, and these patients were almost invariably of the nervous type. There is no denial that severe menopausal symptoms do occur after radiation menopause. The number of such cases, however, is small and possibly no greater than the number of patients experiencing the same symptoms after normal menopause. It is difficult to determine the exact percentage of women having severe symptoms following normal menopause; but Keene and Block[9] have estimated it at from 5 to 10 per cent.

Our group of patients included many physicians' wives, nurses, school teachers and business women. We have not observed a single instance in this group of patients wherein a woman was unable to continue with her routine duties. Those patients who have ample time to think about their nervous discomfort or who perhaps have attending physicians who never overlook the opportunity of applying routine menopausal therapy are likely to have the most difficulty with menopausal symptoms. It has been our experience that the majority of these women later felt that any attendant nervous discomfort

TABLE 1.—*Small Tumors, Size of Three Months' Pregnancy or Smaller*

	Number	Percentage
Total number of cases	722	
Patients without pressure symptoms	685	94.9
Patients with pressure symptoms	37	5.1
Percentage of relief of pressure symptoms	33	89.2
No change in size of tumor	5	0.7
Fifty per cent reducation in size of tumor	25	3.5
Slight enlargement of uterus remaining	66	9.1
Complete reduction—uterus normal	609	84.3
Patients operated on later	17	2.4
Normal or only slight enlargement of uterus remaining	675	93.5

was more than compensated for by the simplicity of the procedure which removed the fibroid tumor with its uncomfortable symptoms.

The determination of the effect of the menopause on sexual function is a difficult problem. A definite effort was made to obtain information on this subject and, although a complete statistical analysis cannot be given, the majority of the married patients were interrogated, and nearly all cooperated in discussing the matter. Only 10 patients stated definite loss of sexual desire, 4 of these later reporting a return to normal after the general health improved. No evidence was presented to show that the disturbance of sexual function following irradiation menopause differed from that following surgical or normal menopause. A patient should not be told that irradiation will unsex her. That no greater fallacy exists has been shown by all observers who have studied large groups of cases.

TABLE 2.—*Total Large Tumors, Size of Four Months' Pregnancy or Larger*

	Number	Percentage
Number of cases	264	
Patients without pressure symptoms	138	52.3
Patients with pressure symptoms	126	47.7
Percentage of relief of pressure symptoms	82	65.0
No change in size of tumor	11	4.2
Twenty-five per cent reduction in size of tumor	13	4.9
Fifty per cent reduction in size of tumor	62	23.5
Seventy-five per cent reduction in size of tumor	28	10.6
Slight enlargement of uterus remaining	42	15.9
Complete reduction—uterus normal	97	36.7
Patients operated on later	11	4.2
Normal or only slight enlargement of uterus remaining	139	52.7

In our series dyspareunia has been observed in 7 patients. It is known that this condition occurs in some instances after the mechanical defects due to a complete or subtotal hysterectomy, and because of atrophic changes in the vaginal mucosa it sometimes follows normal menopause.

Another fact which convinces us that irradiation menopause does not differ from the normal is that in more than 1,000 patients with carcinoma of the uterus whom we have treated with irradiation, regardless of the age of the patient, little complaint was made about the irradiation menopause.

It is our policy not to use any type of endocrine therapy for alleviation of menopausal symptoms in patients with carcinoma of the uterus. In this group, the number of patients with severe menopausal symptoms has been too small to be of any practical importance—certainly no more than would be found after normal menopause.

AFTER-EFFECTS OF RESIDUAL TUMOR MASSES

According to Schreiner,[10] the size of the tumor in his series of patients was definitely influenced by radiation therapy in 85 per cent, there having been either regression to normal or a diminution to 50 per cent of the original size, and 95.5 per cent became symptomatically well.

In his report on 130 patients with uterine fibromyomas larger than a 3 months pregnancy treated by radiation therapy, Corscaden[11] found complete shrinkage in 63.4 per cent, reduction in size to one fourth in 23.2 per cent, to one half in 6.3 per cent and to slight but unsatisfactory dimensions in 4.5 per cent; no reduction occurred in the size of the mass in 2.6 per cent of the cases. In some patients with large tumors, malignant changes later occurred.

Neill[12] reported disappearance of the tumor in 80 per cent of the smaller fibromyomas and in 50 per cent of the larger ones. Burnam[8] observed that more than 60 per cent of the large tumors disappear after radiation therapy. Little evidence exists to substantiate the belief that a small, residual, symp-

7. Norris, C. C., and Behney, C. A.: Am. J. Obst. & Gynec. **32**: 661 (Oct.) 1936.
8. Burnam, C. F.: Am. J. Roentgenol. **37**: 234 (Feb.) 1937.
9. Keene, F. E., and Block, F. B.: Am. J. Obst. & Gynec. **17**: 848 (June) 1929.
10. Schreiner, B. G.: Radiology **16**: 44 (Jan.) 1931.
11. Corscaden, J. A.: Am. J. Roentgenol. **29**: 511 (April) 1933.
12. Neill, William, Jr.: West Virginia M. J. **31**: 71 (Feb.) 1935.

tomless tumor will later cause any difficulty to the patient. Inflammatory degeneration of remaining fibroid masses is rare. In our experience, fibroid tumors the size of a 4 months pregnancy or larger are the only ones in which this has occurred, and we have observed only two such instances. Large, irregular, or multiple pedunculated tumors are more likely to degenerate, and consequently patients with these should be operated on if possible.

The determination of the size of the tumor by bimanual examination cannot be entirely accurate, and it is really a matter of estimation. The size of the tumors in our series varied from that of a 3 months or less to that about the size of an 8 months pregnancy. No case was included unless the uterus was either definitely enlarged to at least twice normal size or, although the uterus was small, definite nodules could be palpated proving the tumor to be a true fibroid.

In ascertaining the decrease in size after treatment, the estimations of 25 per cent, 50 per cent and 75 per cent reduction used in the large tumor group are probably open to question, but these calculations were made after examination. The after-treatment group designated as "slight enlargement of uterus remaining" included those patients in whom a slight irregularity or nodulation of the fundus could be felt or in whom the uterus was still enlarged less than twice its normal size.

Tables 1 and 2 are self explanatory and show the effect of irradiation in regard to reduction in size of the tumor in the various groups, the number of patients operated on, the occurrence of pressure symptoms and the percentage of relief. The size of the tumor and the number of cases of each type are as follows: 3 months' pregnancy or less, 722; 4 months' pregnancy, 149; 5 to 6 months' pregnancy, 107; 7 to 8 months' pregnancy, 8.

CANCEROUS DEVELOPMENT IN THE UTERUS AFTER RADIATION THERAPY

There is no evidence to lead one to believe that uterine cancer occurring after radiation therapy is a serious consideration. This occurred in only 4 cases in our series (table 3). This number is probably well within the normal limits of carcinoma in an age group comparable to our series of patients, three fourths of whom are in the "cancer age." In this group, in 3 patients carcinoma of the fundus developed three months, one year and five years respectively after radiation therapy, and one patient suffered carcinoma of the cervix six years after treatment. A larger percentage of other types of carcinoma than carcinoma of the uterus occurred. In 6 patients there developed later carcinoma of the breast, in 1, of the kidney, and in 1, of the stomach. Norris and Behney [7] found that in only 7 out of 485 patients previously treated by irradiation did carcinoma develop. Macfarlane [13] observed that the incidence of carcinoma was only 0.35 per cent in 3,890 patients treated by irradiation in German clinics, whereas cancer may occur normally in as high as 5 per cent of women in the "cancer age." Sarcomatous degeneration is very rare. In 112 patients with large tumors Corscaden [11] found no late sarcomatous degeneration. Pfahler [14] has even suggested that irradiation may afford a distinct protection against later development of cancer in the uterus. It is well known that carcinoma occasionally occurs in a cervical stump after supravaginal hysterectomy (2 per cent in Polak's series and 0.27 per cent in Hochman's series [15]). From our experience and from available data there is little reason to believe that cancer is more likely to develop in the uterus remaining after radiation therapy than in the remaining cervical stump after hysterectomy or in the normal uterus of any woman in the "cancer age."

TABLE 3.—*Patients Operated On After Radiation Therapy (Tumor Size of Three Months' Pregnancy or Smaller)*

Total number of cases.....17 or 2.4%

Number of Cases	Findings and Indications
3	Ovarian cyst: size of tumor unchanged and pressure remained
3	Submucous fibroids: bleeding continued
3	Carcinoma of the fundus: bleeding later: 3 months, 1 year and 5 years after treatment
1	Carcinoma of cervix: developed 6 years after treatment
1	Intestinal obstruction: 3 years after treatment (tumor adherent to intestine)
2	Carcinoma of ovary: irregular bleeding continued
4	Tumors remaining without relief of pressure symptoms

TABLE 4.—*Patients Operated On After Radiation Therapy (Tumor Size of 4 Months' Pregnancy or Larger)*

Total number of cases.....11 or 4.2%

Number of Cases	Findings and Indications
7	Symptoms of pressure or bleeding not relieved
1	Ovarian cyst: masses increased in size
1	Dermoid cyst: large mass removed
2	Degeneration (inflammatory) of fibroid mass occurred

Tables 3 and 4 show the cases in which operation was later performed, together with indications for operation and the findings. It can be seen that an incorrect diagnosis was the reason for the majority of failures. Fortunately the group is small. In my entire series of 986 cases operation was necessary in only 2.8 per cent.

SUMMARY

1. An analysis was made of 986 patients with uterine fibromyoma treated by radiation therapy between 1927 and 1937, with a follow-up period of from two and one-half to twelve and one-half years.

2. Correct diagnosis should be established before radiation treatment is commenced; if doubt exists as to diagnosis, operation is the treatment of choice.

3. Some contraindications to radiation treatment of uterine fibroid tumors are definite and should be followed; others are possibly too rigid to be exactly substantiated, and patients for radiation therapy are probably being selected too conservatively.

4. The average age of our group is 42.5 years, approximately 75 per cent of the patients being over 40 and, therefore, in or near the menopausal age. We believe that irradiation menopause is no more troublesome than normal menopause. Sexual function is not destroyed.

5. Preexisting pelvic inflammation is not a justifiable contraindication to radiation therapy. Acute pelvic inflammation after irradiation occurred in only 1 patient in our series.

6. In only 4 patients (0.4 per cent) did cancer of the uterus develop after radiation therapy. A remaining uterus or residual mass is no more likely to become cancerous than a normal uterus in a woman of the "cancer age."

13. Macfarlane, Catharine: Am. J. Obst. & Gynec. **23**: 108 (Jan.) 1932.
14. Pfahler, G. E.: Am. J. Roentgenol. **31**: 51 (Jan.) 1934.
15. Polak and Hochman, cited by Danforth, W. C.: Am. J. Obst. & Gynec. **28**: 409 (Sept.) 1934.

7. Inflammatory degeneration of large fibroid tumors occurred in 2 patients. In both cases, operation was later carried out successfully.

8. In tumors the size of a 3 months pregnancy or smaller (722 cases), there was a reduction of the uterus to normal in 84.3 per cent and to normal or only slightly enlarged (less than twice normal) size in 93.5 per cent. Only 2.4 per cent of patients with these tumors were later operated on.

9. In patients with tumors the size of a 4 months pregnancy or larger (264 cases) there was a reduction of the uterus to normal in 36.7 per cent and to normal or slightly enlarged (less than twice normal size) in 52.7 per cent. Only 4.2 per cent of this group were later operated on. In tumors of this size roentgen rays alone, preceded by curettage, are the most satisfactory method of radiation therapy.

10. Careful selection of cases is the most important single factor contributing to the success of radiation therapy for uterine fibromyoma.

ABSTRACT OF DISCUSSION

DR. WILLIAM P. HEALY, New York: I should like to commend this paper to all surgeons and gynecologists. It represents an unbiased analysis of a large enough series of cases to indicate what can be done to cure nonmalignant tumors of the uterus in a conservative manner, protecting patients for whom the risk of major surgery may be very grave. There was no mortality in this series of cases. The size of the tumors included is interesting. Some of them were as large as an eight months pregnancy. I endorse the author's statement regarding the diagnosis of the tumor mass. It is interesting that in his report of 986 cases treated by irradiation there was only one case in which some inflammatory disturbance seemed to result from the treatment. We may therefore say that in the hands of competent therapists irradiation may be carried out safely without fear of a complicating inflammatory disturbance. In only 5 per cent of the cases was radium alone the therapeutic agent. In the remaining 95 per cent of the cases, either roentgen rays alone or roentgen rays in combination with radium were used. Actually, 65.5 per cent of the patients were treated with radium plus roentgen rays. My feeling has been that, if the tumor is the size of a three months gestation or larger, roentgen therapy should be combined with the introduction of radium into the uterus. Diagnostic curettage is essential before subjecting the patient to any other form of therapy, because we must rule out a possible cancer in the cervix or corpus. Severe bleeding is best controlled with radium and curettage plus roentgen rays. In the larger tumors roentgen rays are necessary because radium alone will not bring about castration, and if we do not establish castration we shall not terminate the growth of the tumor mass. I would not recommend irradiation for myomatous tumors after the menopause despite the good results obtained in this series of cases, because cancer of the corpus is a common lesion after the menopause, and 38 per cent of my patients with cancer of the corpus have had coincidental myomatous tumors in the uterus. The risk of an error in diagnosis is very grave.

DR. CHANNING W. BARRETT, Chicago: We have heard from the Far West, from the Far East. I ask the privilege of the floor for fear, if the momentum gets started, you will not know there is such a thing as surgery for fibroids of the uterus. Some twenty-nine years ago, I remember a man rushed into the meeting of the gynecologic section at Washington and asked the privilege of the floor; seemingly he could not wait. He said "I hold in my hand a capsule that is going to change gynecology entirely. There will practically be no more operating for fibroids of the uterus." He acted as though anxious to get back and get that capsule working for fear some patient might not receive its benefits. I wondered at the time how much of that was overoptimism. A few years later Gauss of Germany said "I have something that does away with surgery for fibroids of the uterus," and men went over there to see Gauss and his work. They came back and equipped themselves. A good many of them have discarded it. Some of them read papers on their work with fibroids treated with roentgen rays, and now they have discarded them and have no more use for them except in rare cases. There are indications for radium and roentgen rays, and there certainly are indications for surgery. What does one want in this condition? A live patient, certainly: a woman with all her functions left that can be left. If the uterus can be saved, we want to save it. If we can save the ovaries and take out the uterus, we want to save the ovaries, for in them is the estrogenic function which keeps her a woman, the feminizing function. And now we think of irradiation. Is it such a benign thing? It is the most radical thing you can do to a woman; it practically takes out her ovaries and her uterus. There is no conservatism there, and it leaves the fibroid set to degenerate. Degeneration is a crying evil of fibroids and irradiation increases it. What are the real indications for treatment with radium? A woman who is near the menopause who has a small fibroid, bleeding but with no other symptoms, no degeneration and no complications. One cannot treat a woman before the age of 40 with this and do justice to her, because irradiation will destroy her childbearing and ovarian function. If there is a small fibroid present that is giving symptoms, the most conservative thing one can do to the patient is to take out the small fibroid surgically.

DR. ARTHUR H. CURTIS, Chicago: I am rather in accord with the sense of Dr. Barrett's remarks. With added years I find more and more instances in which an apparently simple case of uterine fibroids turns out to be a malignant growth or an ovarian tumor or an endometriosis which would be better treated by surgery than with radiation. I believe this whole problem can be summarized as it is seen by gynecologists throughout America whose opinion, experience and advice we would wish to follow by saying that radiotherapy in these cases is indicated chiefly for women who are at or near the menopause, who have a bleeding tumor of a size not exceeding the uterus of a three or three and one-half months pregnancy; when radiotherapy is given there should always be a preliminary diagnostic curettage.

DR. WILLIAM E. COSTOLOW, Los Angeles: Dr. Healy mentioned the treatment of tumors after the menopause. There was only one case in the series in which this occurred, and the report is given in the paper. This case was cited to indicate that possibly some of the effects of irradiation may be from direct action of the rays on the tumor cells instead of all the effect being due to the action on the ovaries. I presented the results in a large series of cases, the majority having been selected especially for radiation therapy by surgeons and gynecologists, but I did not advocate irradiation for all fibroids. I mentioned that one surgeon in our community had sent me over 200 cases of fibromyoma. Certainly he did not refer all of his fibroid cases for radiation therapy but selected those for which he felt the conservative type of therapy was indicated. Time does not permit me to reply to all the arguments which Dr. Barrett has presented. However, if he will carefully read the paper I have just presented he will there find my answers to most of his contentions. I agree with Dr. Curtis in his remarks about the treatment of young women and very large tumors. As I pointed out in the paper, 75 per cent of the patients were past 40 and in the menopause age, the average age being 42.5 years. The small tumors are the ones which should be selected for radiation therapy; the large tumors frequently cause the radiologist to get into difficulty. Dr. Curtis mentioned the danger of malignancy occurring later if the uterus is not removed. As brought out in my presentation, this occurrence has been less than the normal incidence of uterine cancer, for in 1,009 cases, 986 of which were followed from two and one-half to twelve and one-half years, cancer of the uterus developed later in only 4 cases (0.4 per cent).

THE BODY ECONOMY OF VITAMIN C IN HEALTH AND DISEASE

WITH SPECIAL STUDIES IN TUBERCULOSIS

HENRY C. SWEANY, M.D.
CHARLOTTE LOUISE CLANCY, M.D.
MOLLY H. RADFORD, M.D.
AND
VIOLA HUNTER, M.Sc.
CHICAGO

During the past generation most of the diseases due to a deficiency of accessory food factors have been brought under control, and within the last decade many of the active principles concerned have yielded the secrets of their chemical structure. Not the least of these is the antiscorbutic substance, or "water soluble" vitamin C, a principle known to exist in limes and lemons for over a hundred years and recently found in abundance also in a large number of fruits and vegetables and in animal tissues.

As healing in tuberculosis is characterized largely by the formation of connective tissue, and the latter, according to Wolbach and his associates,[1] is formed by the action of vitamin C on fibroblasts, it does not seem unreasonable to suspect that a vitamin C deficiency may be one of the causes of unfavorable trends in tuberculosis, if it does not actually contribute to exacerbations of the disease. By the same line of reasoning, a replenishment of a deficiency of vitamin C, not to mention its administration in excess, may help at least to change the disease from an unfavorable course to a more favorable one.

With these possibilities in mind, a plan of study of the problem was undertaken which involved many experiments on the economy of vitamin C in health and disease in addition to extensive therapeutic experiments made in a large series of cases of pulmonary tuberculosis.

PREVIOUS WORK WITH VITAMIN C IN TUBERCULOSIS

The report to follow represents only a summary of this combined study. A preliminary phase of the work has already been reported[2] on the results of blood examination during the early period of treatment. A slight hematinic value of vitamin C was found to exist after the beginning of treatment and to persist for the first few months. Although experimental studies[3] show that vitamin C deficiency enhances the development of tuberculosis in guinea pigs, reports in the literature with regard to therapeutic benefits of vitamin C on tuberculosis are not convincing. Petter[4] reports favorably in a series of children, most of whom had surgical or lymph node tuberculosis. He gave the ascorbic acid in a malted milk mixture, without any controls. Hasselbach[5] made an extensive study of the therapeutic value of ascorbic acid on 70 patients with various types of tuberculosis. He especially recommends its use for patients with a tendency to small seeping hemorrhages. Unfortunately, his study was complicated by a simultaneous administration of calcium. He reported that patients with a good prognosis and with no deficiency but stationary in their disease course were benefited. The effect in such cases is reputed to be that of a general tonic. If there is a measurable deficiency, the effect of vitamin C is more obvious. Finally, he combines it with gold therapy, especially when there is a tendency for hemorrhages to develop. Like many others, Hasselbach did not report controls. Sande[6] also recommended its use with gold therapy to reduce the tendency to form hemorrhages.

Heise, Martin and Schwartz[7] found that there was a greater decrease in the sedimentation of red blood cells in treated patients over controls, but that there was no noticeable clinical improvement after treatment with vitamin C.

Sebok and Preztai[8] state that the long continued fever and increased metabolism in tuberculosis causes a depletion in the vitamin C reserve, but that in 20 cases only 2 could be found with true hypovitaminosis. The extreme deficiency is usually from 3 to 4 Gm. The same authors also report that ascorbic acid was given with good results in pulmonary hemorrhages. For a rapid removal of the deficiency large doses of ascorbic acid are given, but lemon juice is used to maintain the normal level after it approaches this level.

Trautwein[9] found that his febrile patients had a vitamin C deficiency of from 1,800 to 3,600 mg., for which he gave from 150 to 200 mg. a day, injected intravenously to restore the level to normal. After such treatment a decided improvement was indicated by a gain in weight, fall of temperature, decrease in red cell sedimentation rate and a favorable trend in the blood pictures. Liver function improved as the result of a more favorable effect on the storage of glycogen. Bauer and Vorwerk,[10] however, treated a series of patients and concluded that a "final judgment of the therapeutic value of vitamin C in tuberculosis cannot yet be passed."

From the Research Department of the City of Chicago Municipal Tuberculosis Sanitarium, Dr. Frederick Tice, president, Board of Directors (Dr. Sweany) and the Department of Physiology, University of Chicago, Dr. A. J. Carlson, chairman (Dr. Clancy, Dr. Radford and Miss Hunter).

Read before the Section on Pathology and Physiology at the Ninety-First Annual Session of the American Medical Association, New York, June 14, 1940.

Dr. Eugene deSavitch was largely responsible for suggesting this study and also for obtaining financial assistance from the California Fruit Growers Exchange. Generous subsidies were received from the California Fruit Growers Exchange. Mr. A. J. Lorenz not only helped to negotiate the subsidies but assisted with many technical details of analysis. Dr. Frederick Tice cooperated in carrying out the work at the Chicago Municipal Tuberculosis Sanitarium. Dr. A. J. Carlson gave sound advice. Mr. Charles Steinmetz assisted with the chemical analyses.

1. Wolbach, S. B., and Howe, P. R.: Intercellular Substances in Experimental Scorbutus, Arch. Path. **1:** 1 (Jan.) 1926. Wolbach, S. B.: Controlled Formation of Collagen and Reticulum: Study of Source of Intercellular Substance in Recovery from Experimental Scorbutus, Am. J. Path. (supp.) **9:** 689, 1933; Pathologic Changes Resulting from Vitamin Deficiency, J. A. M. A. **108:** 7 (Jan. 2) 1937. Menkin, Valy; Wolbach, S. B., and Menkin, M. F.: Formation of Intercellular Substance by Administration of Ascorbic Acid (Vitamin C) in Experimental Scorbutus, Am. J. Path. **10:** 569 (Sept.) 1934.

2. Radford, Molly; de Savitsch, E. C., and Sweany, H. C.: Blood Changes Following Continuous Daily Administration of Vitamin C and Orange Juice to Tuberculous Patients, Am. Rev. Tuberc. **35:** 784 (June) 1937.

3. Grant, A. H.: Effects of Rachitic Diets on Experimental Tuberculosis, Am. Rev. Tuberc. **21:** 115 (Jan.) 1930. Höjer, J. A.: Scurvy, Acta pædiat. (supp.) **3:** 8, 1924. Heymann, B.: Experiments on Guinea Pigs on Relations Between Scurvy and Chronic Tuberculosis, Klin. Wchnschr. **5:** 59 (Jan. 8) 1926. Leichtentritt, B.: Accessory Nutrients and Bacterial Growth, Monatschr. f. Kinderh. **22:** 375 (Nov.) 1921. Zilva, S. S.: The Behavior of *l*-Ascorbic Acid and Chemical Compounds in the Animal Body: Antiscorbutic Activity in Relation to Retention by Organism, Biochem. J. **29:** 1612, 1935. Greene, Meridian R.; Steiner, Morris, and Kramer, Benjamin: Role of Chronic Vitamin C Deficiency in the Pathogenesis of Tuberculosis in the Guinea Pig, Am. Rev. Tuberc. **33:** 585 (May) 1936. de Savitsch, Eugene; Stewart, J. D.; Hanson, Louise, and Walsh, E. N.: Influence of Orange Juice on Experimental Tuberculosis in Guinea Pigs, Nat. Tuberc. A. Tr. **30:** 130, 1934.

4. Petter, C. K.: Vitamin C and Tuberculosis, Journal-Lancet **57:** 221 (May) 1937.

5. Hasselbach, F.: Role of Vitamins in Therapy of Tuberculosis, Klin. Wchnschr. **16:** 472, 1937.

6. Sande, H.: Gold Therapy and Vitamin C, Klin. Wchnschr. **17:** 1745 (Dec. 10) 1938.

7. Heise, F. H.; Martin, G. J., and Schwartz, Spencer: The Influence of the Administration of Vitamin C on Blood Sedimentation and Sensitivity to Tuberculin, Brit. J. Tuberc. **31:** 23 (Jan.) 1937.

8. Sebok and Preztai: Vitamin C Deficiency in Tuberculosis, Tuberculosi, 1937, no. 12.

9. Trautwein, Herbert: Cevitamic Acid Therapy of Pulmonary Tuberculosis, Beitr. z. Klin. d. Tuberk. **91:** 411, 1938.

10. Bauer, George, and Vorwerk, Wolfgang: Vitamin C Deficiency in Pulmonary Tuberculosis, Beitr. z. Klin. d. Tuberk. **91:** 262, 1938.

Its action, if any exists, is not specific but improves the general conditions.

In order more completely to understand the role of vitamin C in tuberculosis, it seemed desirable to know many facts concerning its economy in health and disease.

THE NORMAL DAILY REQUIREMENTS OF VITAMIN C

Most of the earlier studies devoted to the determination of the daily requirement of vitamin C were based on a quantity required to prevent gross clinical symptoms. According to the work of Harris and his co-workers [11] from 25 to 35 mg. is the minimum amount for normal persons. Most workers, however, claim that from 55 to 60 mg. a day is more nearly the optimum quantity for a good state of health, although much less may prevent scurvy. Van Eekelen's [12] figure of 0.84 mg. and Heinemann's [13] of 0.85 mg. per kilogram, amounting to about 60 mg. a day, are accepted as the optimum minimum by most experienced workers. The low level recommended by Harris (25 to 35 mg.) may be considered as an indispensable minimum to prevent the first sign of scurvy, while the higher level (50 to 60 mg.) is more nearly the optimum to maintain a good state of health. It is being recognized that patients do not need to be scorbutic to suffer from avitaminosis C. King [14] says "The fact that there is a wide zone of vitamin C deficiency between scurvy and optimum health, is of more interest in relation to human health than the problem of clinical scurvy." Rinehart and Mettier [15] state that a depressed ascorbic acid level may be a "necessary background for rheumatic fever." Although the optimal daily requirement has been established, it furnishes only a starting point for a determination of the daily balance and a total quantity of vitamin C in the body.

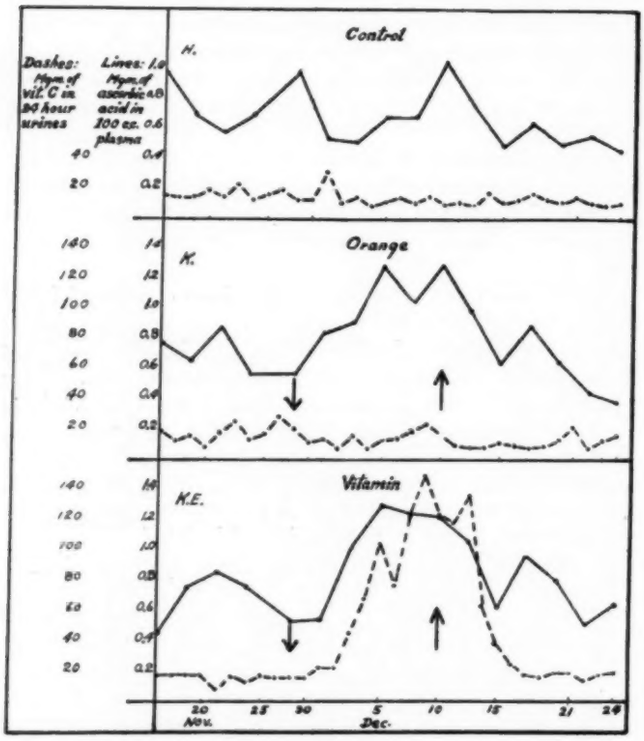

Chart 1.—Course in three representative cases showing one control (H). Note that the level in the urine fell from about 15 to 11 mg. in twenty-four hours and the blood from 1.0 to 0.6 mg. One of the orange group (K) failed to saturate after the administration of 2,750 mg. extra ascorbic acid. The blood curve rose promptly but soon fell when the ascorbic acid was stopped. The urine curve did not rise at all. One subject received ascorbic acid (vitamin) who showed nearly normal saturation (K. E.).

THE DAILY REQUIREMENTS OF VITAMIN C IN TUBERCULOUS INDIVIDUALS

Heise and his associates,[16] Trautwein,[9] and others have recommended rather empirically the administration of from 150 to 200 mg. of vitamin C a day in severe tuberculosis to care for the requirements, but no accurate daily balance has yet been worked out.

To help solve this problem, many experiments were performed, some of which will be reported. Both early and advanced cases were studied. In the early cases there was but little unsaturation and they are omitted in this report. A summary of the results in the far advanced B and C cases, consisted of 30 cases arranged as follows: Five men and 5 women were studied for six weeks to establish a normal "base line" for our diet; another similar group was run for two weeks, then given orange juice containing approximately 250 mg. of ascorbic acid for a period of two weeks; and then for two weeks the blood and urine were allowed to return to the base line. The third similar group received 250 mg. of crystalline vitamin C in twenty-four hours in the second two weeks instead of the orange, to see if there were substances in oranges that behaved differently from the pure substance. The blood and urine observations of representative cases of each group are shown in chart 1.

Representative controls of both men and women revealed a blood content of around 0.8 mg. per hundred cubic centimeters of blood at the beginning of the experiment, which underwent a slow decrease on the general diet to about 0.5 mg. after about four weeks and a much slower drop after that. The corresponding urine curve ranges from about 18 mg. at the beginning to about 10 mg. in twenty-four hours during the same interval. The general diet proved to be inadequate in vitamin C because there is a slow fall of the blood and urine curves after the beginning of the experiment to levels that are reported by van Eekelen,[12] Harris [17] and others to represent unsaturation.

The orange and vitamin blood curves were generally sufficiently alike to describe together. There was a slight drop at first from about 1.0 to 0.6 mg. per hundred cubic centimeters of blood. After the beginning of the administration of the vitamin-containing drinks the blood curve rose sharply for about four days to about 1.5 mg. and remained at this level until the treatment was stopped. The curve then began to return toward the normal, at first quickly, then slowly, over a period of ten to twelve days.

In the majority of cases the urine curves began to rise from the base line about four to six days after the rise in the blood curve, suggesting that there was from 750 to 1,250 mg. of unsaturation if no allowance was

11. Harris, Leslie J.; Abbasy, M. A.; Yudkin, John, and Kelly, Simon: Vitamins in Human Nutrition; Vitamin C Reserves of Subjects of Voluntary Hospital Class, Lancet **1**: 1488 (June 27) 1936.

12. van Eekelen, Marie: On the Amount of Ascorbic Acid in Blood and Urine, Biochem. J. **30**: 2291 (Dec.) 1936.

13. Heinemann, Martin: On Relation Between Diet and Urinary Output of Thiosulfate and Ascorbic Acid: Human Requirements for Vitamin C, Biochem. J. **30**: 2299, 1936.

14. King, C. G.: Vitamin C: Ascorbic Acid, Physiol. Rev. **16**: 238 (April) 1936.

15. Rinehart, J. F., and Mettier, S. R.: Partial Vitamin C Deficiency and Its Relation to Rheumatism, Am. J. Path. **9**: 952 (Nov.) 1933.

16. Martin, G. J., and Heise, F. H.: Vitamin C Nutrition in Pulmonary Tuberculosis, Am. J. Digest. Dis. & Nutrition **4**: 368 (May) 1937.

17. Harris, L. J., and Ray, S. N.: Diagnosis of Vitamin C Subnutrition by Urine Analysis, with Note on Antiscorbutic Value of Human Milk, Lancet **1**: 71 (Jan. 12) 1935. Abbasy, M. A.; Harris, L. J.; Ray, S. N., and Marrack, J. R.: Diagnosis of Vitamin C Subnutrition by Urine Analysis: Quantitative Data; Experiments on Control Subjects, ibid. **2**: 1399 (Dec. 12) 1935.

made for any destruction of the vitamin C. The quantity mounted sharply to from 140 to 220 mg. and then "leveled off," forming a few peaks, and decreased abruptly from two to four days after the treatment was stopped. It was near the base line in another four days. The high level reached is from 60 to 150 mg. less than the total intake.

These conditions prevailed among 6 women and 3 men. Two other cases showed irregular curves and a slight lag before appearing in the urine in from six to eight days (from 1,500 to 2,000 mg. unsaturation). Of 2 men the kidney threshold was not reached until eight and ten days respectively (from 2,000 to 2,500 mg. unsaturation), when a slight amount appeared in the urine. Two subjects, 1 man and 1 woman, showed no increase at all in the urine, indicating that they were not saturated enough to spill vitamin C in the urine even after receiving 250 mg. a day of extra ascorbic acid for eleven days (2,750 mg.). The blood content rose in all cases to the usual level, which proved that the ascorbic acid was not destroyed in the gastrointestinal tract.

Over and above the low intake in the general diet the rate of unsaturation seemed to vary roughly with the acuteness and extent of the disease. Two subjects became almost completely unsaturated in eleven days. Judging from van Eekelen's work,[12] the unsaturation in these cases on a diet containing 31 mg. of ascorbic acid occurred in about one-fourth the time it took to unsaturate normal human beings on a vitamin C free diet.

Similar conclusions have been shown by Heise and Martin,[16] Trautwein [9] and others.

UNSATURATION DUE TO LACK OF INTAKE ASSOCIATED WITH CERTAIN TUBERCULOUS PATIENTS

Another study was undertaken in certain complications and associated diseases in which a vitamin C deficiency might be expected as the result of a lack of intake in addition to the activity of the disease. In addition, it was desirable to remove the objection concerning the destruction of vitamin C in the gastrointestinal tract following administration by mouth.

A rapid and direct method of testing unsaturation recommended by Barron [18] was used, so that the status of a patient at any time could be ascertained with reasonable certainty. Instead of using sodium ascorbate, however, 500 mg. of ethyl-amine-ascorbate (cenolate-Abbott) was injected slowly intravenously and the urine tested after six hours for total vitamin C, after the method of Goldsmith and Ellinger.[19] According to Barron's method, a recovery of less than 10 per cent in twenty-four hours represents unsaturation. Goldsmith and Ellinger found that about 60 per cent of the total injected is eliminated within six hours. Wright and his associates [20] have contributed the added information that the elimination is much slower in nephritis with retention. If 5 per cent or more, therefore, is eliminated within six hours and the patients are found to be free from nephritis, there should be no detrimental unsaturation.

The results revealed that nearly 70 per cent of the series selected were partly or wholly unsaturated. Of 26 subjects, 3 were completely unsaturated (below 5 per cent recovery), 8 were poorly saturated (6 to 15 per cent recovery), 7 partly saturated (16 to 30 per cent recovery) and 8 "adequately" saturated (30 to 68 per cent recovery).

The unsaturated or poorly saturated subjects were all on a poor vitamin C intake. One alcoholic addict with terminal tuberculosis was absolutely unsaturated. The patients on "nonresidue" and "general" diets for enteritis were also low. One peptic ulcer patient was unsaturated, another was low, but two others were surprisingly high.

A group of 15 critically ill patients was similarly studied with even more striking results, because in the last thirty days of life there is frequently little or no food eaten. Two subjects ran regularly between 0.3 and 0.4 mg. per hundred cubic centimeters of plasma with the urine running lower than 8 mg. in twenty-four hours. One of these patients was studied on till death, after which the organs were analyzed for vitamin C. Seven days before death she was given 500 mg. of ethyl-amine-ascorbate intravenously on three successive days without any appreciable rise of vitamin C in the urine. As determined in later experiments, 1.5 Gm. should about saturate such a patient weighing 30 Kg. because in saturated bodies there are about 5 mg. per hundred grams of body weight.

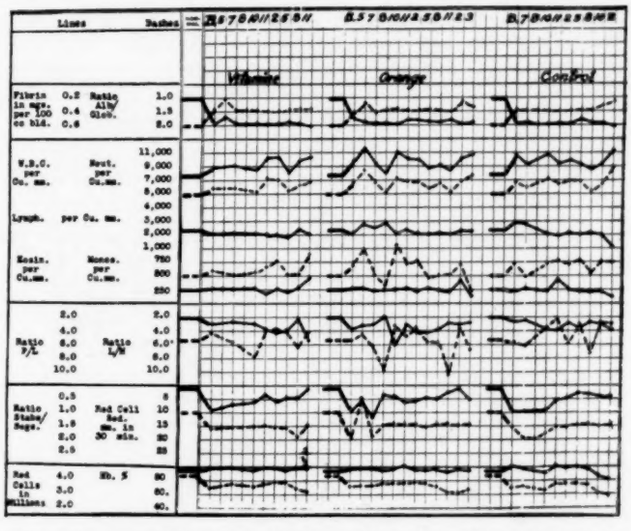

Chart 2.—Composite curves of various blood observations of the three groups of patients of main group 1. Outside of a terminal drop in lymphocytes (fifth curve from the top) and the hemoglobin and red cells (last two curves) the three groups are practically the same. The solid line and the dashes start from a normal reading on the left and lead to the first result and then on to the end, a total of about fourteen months.

As an approximate calculation gave 0.650 Gm. of vitamin C in the body at death, there was almost a gram, or 60 per cent of the theoretic total, that was destroyed or diverted during the course of the experiment.

In summarizing, the causes of unsaturation in tuberculosis are the destruction of the vitamin C by the disease, the lack of intake due to a low vitamin C diet, the restriction as a result of therapy of peptic ulcer, colitis and so on, and the voluntary restriction due to lack of appetite or alcoholism, or to a combination of two or more of these conditions.

ESTIMATION OF THE TOTAL VITAMIN C IN THE BODY

Several methods of approximating the total body content have been attempted. The oldest one perhaps is the one that involves the time required to produce

18. Barron, E. S. G.; Brumm, H. J., and Dick, G. F.: Ascorbic Acid in Blood and Urine After Intravenous Injection of Sodium Ascorbate, J. Lab. & Clin. Med. **23:** 1226 (Sept.) 1938.

19. Goldsmith, G. A., and Ellinger, G. F.: Ascorbic Acid in Blood and Urine After Oral Administration of Test Dose of Vitamin C; Saturation Test, Arch. Int. Med. **63:** 531 (March) 1939.

20. Wright, Irving S.; Lilienfeld, Alfred, and MacLenathen, Elizabeth: Determination of Vitamin C Saturation: A Five Hour Test After an Intravenous Test Dose, Arch. Int. Med. **60:** 264 (Aug.) 1937.

scurvy, multiplied by the daily elimination. It has been found to require about ninety days in man to reach the scorbic state. Assuming, therefore, that from 10 to 20 mg. a day is eliminated in the urine and a comparable quantity eliminated in the sweat and feces, there would be a loss of between 1,800 and 3,600 mg., an amount consistent with the estimate of Trautwein [9] and of Sebok and Preztai.[8]

Another method is just the reverse of the preceding, viz., the amount necessary to saturate an unsaturated individual. The work of van Eekelen [12] reveals that in a decidedly unsaturated person it requires from 2 to 4 Gm. of vitamin C before any appreciable amount appears in the urine.

THE RESULTS OF ANALYSIS OF ORGANS FOR VITAMIN C

Although no record of a complete assay of the vitamin C of the whole body has been made, the content of separate organs has been determined by Yamagami [21] and Birkhaug [22] in guinea pigs and by Yavorsky, Almaden and King [23] in both guinea pigs and organs from a large number of human autopsies. In these reports the adrenals have been shown to possess the highest amount of ascorbic acid (about 0.5 mg. per gram of tissue). The larger organs (brain, liver, lungs,

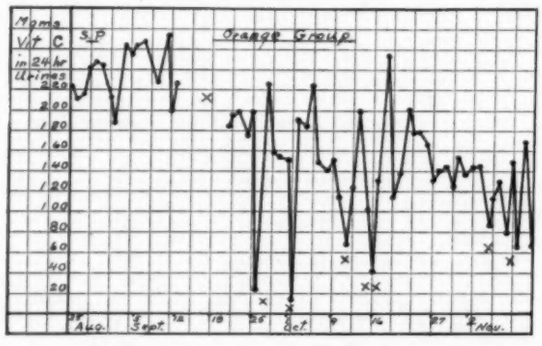

Chart 3.—A midsection of a curve of one of the vitamin cases of the second mass experiment. Note that the curve on the left has as high as 250 mg. elimination a day in the urine, but it drops to 140 mg. near the end. The intake during that time was at least 300 mg. a day. The crosses indicate the days on which treatment was not given.

spleen, kidneys) are lower in content but seem to be more important depots of the body because of their size. These organs have from 0.1 to 0.4 mg. per gram of tissue.

By availing ourselves of the standard table of tissue weights of Vierordt [24] it may be crudely estimated from the reported studies on vitamin C in organs that there are from 3 to 6 Gm. of total ascorbic acid in the normal young adult human body.

AN ATTEMPT TO DETERMINE THE TOTAL VITAMIN C IN THE BODY

In order to test these rough figures for "saturated" persons and see if the total amount of vitamin C could be found in different diseases, especially tuberculosis, analyses were performed on the organs and tissues of 32 bodies coming to autopsy. Because of a lack of space, histories of the patients and detailed analyses are omitted. All but 1 case (a monocytic leukemia) presented some form of tuberculosis. Two of the cases showed diabetes, in one of which also there was myocarditis, and some showed amyloidosis as well as the tuberculosis. One patient died suddenly in a pulmonary hemorrhage, after the disease was nearly arrested.

Bessey's [25] method for tissue analysis was used, but care was taken to keep the p_H below 1.5. Over that figure a complete recovery was not possible in certain tissues, as liver and spleen. The difficulty was overcome by using 7 per cent metaphosphoric acid instead of the 3 per cent advocated in the original method. Duplicates were run on many specimens by Bessey and King's [26] trichloroacetic method. The "tough" tissues, especially skin, were frozen in liquid nitrogen and pulverized according to the method of Graeser, Ginsburg and Friedmann.[27] Duplicate analyses were run on most specimens. The results are arranged roughly in the order of the tissue content of vitamin C.

The "vital tissues" were found to contain the most vitamin C. Hypophysis, adrenal, gonads, pancreas, spleen, liver and brain contain the substance, ranging from about 50 to 90 mg. in the first three to about 20 to 40 mg. per hundred grams of tissue in the last four. The largest depots of the body, however, are muscle and fat, with bone and skin also playing a role. In advanced disease these tissues lose nearly all their reserve and the bulk of vitamin C is found in the brain and liver, although the more vital cells still have the highest concentration. By using Vierordt's [24] standard tables of tissue weights we estimated the content of the bones and muscles. The content of the skin was determined by a special method to be reported later, based on Benedict's tables of the body area. Other tissues were estimated directly or by difference.

The results indicate that advanced active tuberculosis is devastating on the vitamin C reserve, reducing the total quantity to less than 300 mg. even on a fair vitamin C intake. On the other hand in a fatal case of monocytic leukemia there was 2,725 mg. (70 per cent saturation) at death. Another well nourished patient with quiescent fibroid tuberculosis with mild diabetes, who was on a high vitamin C diet, had 3,670 mg., or about 5 mg. per hundred grams of body tissue. These last figures were used arbitrarily as a saturation limit. The other cases ranged in between the two extremes and varied roughly with the intake of vitamin C.

THE EFFECT OF VITAMIN C ON THE DISEASE TUBERCULOSIS

The preceding preliminary studies, as well as the reports of others, justified a trial of vitamin C on various types of tuberculous patients. Although most authors agree that there is an increased requirement, there is no uniform opinion regarding the therapeutic value of vitamin C in tuberculosis. When viewed critically there are few therapeutic attempts that are free from objection on one point or another. Most of the reports suffer from a lack of controls, which is serious in a disease in which, according to Braeuning [28] about

21. Yamagami, Shigeru; Nomura, Kiyoshi, and Nishigaki, Meiji: Vitamin C of the Lung in Experimental Tuberculosis, Kekkaku (Abstr. Sect.) **13:** 42 (Dec. 24) 1935.

22. Birkhaug, K. E.: Role of Vitamin C in Pathogenesis of Tuberculosis in Guinea Pigs: Daily Excretion of Vitamin C in Urine of *l*-Ascorbic Acid Treated and Control Tuberculous Animals; Vitamin C Content of Suprarenals of *l*-Ascorbic Acid Treated and Control Tuberculous Animals, Acta tuberc. Scandinav. **12:** 89, 1938.

23. Yavorsky, Martin; Almaden, Philip, and King, C. G.: The Vitamin C Content of Human Tissues, J. Biol. Chem. **106:** 525 (Sept.) 1934.

24. Vierordt, Herman: Anatomische, physiologische und physikalische Daten und Tabellen, ed. 3, Jena, Gustav Fischer, 1906.

25. Bessey, O. A.: Vitamin C: Methods of Assay and Dietary Sources, J. A. M. A. **111:** 1290 (Oct. 1) 1938.

26. Bessey, O. A., and King, C. G.: Distribution of Vitamin C in Plant and Animal Tissues, and Its Determination, J. Biol. Chem. **103:** 687 (Dec.) 1933.

27. Graeser, J. B.; Ginsburg, J. E., and Friedmann, T. E.: A Method for the Analysis of Tissues, J. Biol. Chem. **104:** 149 (Jan.) 1934.

28. Braeuning, H.: Studies of Series of Roentgenograms as Means of Determining Time of Onset of Tuberculosis in Adults, Ztschr. f. Tuberk. **64:** 416, 1932.

30 per cent heal spontaneously without any treatment whatever. Another objection to the work already reported is that with few exceptions the reports do not include enough cases to rule out the variability inherent in the disease.

SELECTION OF PATIENTS

In order to approach an ideal experimental result, the patients were carefully selected, grouped and evenly matched as to quality and quantity of the disease.

The first consideration was with regard to the natural status of the patient. This included age, sex, race, environment and constitutional factors, each of which was appraised numerically with arbitrary values and recorded on a special chart for that purpose.

Laboratory examinations, especially blood counts and chemistry, careful roentgenologic studies and clinical observations were recorded throughout the three successive mass experiments, one of which will be presented.

THE FIRST MASS THERAPEUTIC EXPERIMENT

The details of the selection were as follows: There was a group of 111 cases chosen, from which 102 were finally selected for the experiment and 98 actually used. These cases were divided into three groups as impartially as possible. First the patients were matched as closely as possible with respect to age, sex, and the various factors considered under the "natural handicap" including the many groups described before. From those nearest alike and having approximately the same "handicap," groups of 3 were chosen. Each group of 3 was arranged in three main columns according to the first letter of their names. Those having the highest letter of the alphabet were to receive daily, in addition to the general hospital diet, 500 cc. of a synthetic orange flavored preparation to which was added an amount of crystalline vitamin C equivalent to the amount of vitamin C in the same volume of fresh orange juice. Those next highest in the alphabet were to receive daily, in addition to the general hospital diet, 500 cc. of freshly prepared orange juice. Those having the lowest letter in the alphabet were to receive daily, in addition to the general hospital diet, 500 cc. of the synthetic orange flavored preparation without vitamin C. This was to constitute the control group.

The 102 patients were started on therapy in May 1935. In September 1935 it was necessary to add 17 patients to replace those who had died or been discharged from the sanatorium. Those who were thus rejected were patients who did not receive any treatment at all. Only 98 were finally carried into the experiment, of which 60 remained to the end. There were 34 controls in the beginning with 14 remaining to the end; 33 in the orange group, 23 of which remained to the end; and 31 in the vitamin group, with 23 remaining to the end. The heavy casualties in the control group before the experiments passed the six months period is significant.

Of the rejected cases, 11 for each of the orange and vitamin and 20 for the controls, 6, 5 and 6 respectively were rejected because of interference such as going home, the institution of some other treatment, death, or other events that caused a termination of the case before three months had elapsed. This type of "casualty" was about equal in all three groups.

The remaining cases of 5, 6 and 14 respectively were followed for more than three months. Most of them were discontinued before six months. A few were carried longer, but because of some failure to get all the studies performed or some interference in the form of special diets they were rejected.

Of the 5 cases of the vitamin group, 2 were on the favorable side and 3 unfavorable, in 2 of which death occurred. Of the orange group there was one on the favorable side and 5 unfavorable, with three deaths. For the controls there were only 2 favorable against 12 unfavorable results, with seven deaths. Of the results on rejected cases of the three mass experiments, 51 per cent of the controls were unfavorable with 31 per cent deaths. The vitamin had 28 per cent unfavorable with 21 per cent deaths, and the orange group 31 per cent unfavorable with 21 per cent deaths.

The cases that were carried on into the experiment were then compared by every available means.

RESULTS OF TREATMENT

In analyzing the charts at the end of the experiment there is so much similarity of the three groups that they are practically interchangeable. While there was a greater number of cases in the orange and vitamin groups showing a favorable hematinic effect, as shown in the first report,[2] the average loss or gain was not sufficient to record by any laboratory means over the whole course of treatment.

An empirical method of calculation revealed also that there was little change roentgenologically between the composite figures of the three groups.

As to the clinical results, the weight gain or loss is the only factor that gives any precise information that can be tabulated. The patients remaining to the end who were not molested in some way by treatment or other interferences were compared in the table.

Of 23 patients remaining on orange, 10 (43.4 per cent) gained weight, 2 (8.7 per cent) were stationary and 11 (47.9 per cent) lost. In the vitamin group only 7 (30.4 per cent) gained; 9 (39.2 per cent) were stationary and 7 (30.4 per cent) lost. The controls had 4 (28.5 per cent) gain, 4 (28.5 per cent) stationary, and 6 (42.0 per cent) lost, respectively. The net result from this particular analysis reveals a similarity of all three groups.

THE SECOND MASS THERAPEUTIC EXPERIMENT

As stated previously, two more mass experiments were carried out in slightly earlier cases than the ones just described. In the second, there were 80 cases compared with 39 (12 controls, 13 orange and 14 vitamin) followed more than one year. There was no essential difference, however, in the final result. A sample chart of the second mass experiment is shown. The results may be interpreted as follows: In the controls the levels revealed saturation in most of the cases, but a few dropped to "unsaturation" levels. In most of the orange and vitamin groups there was a recovery in the urine of a maximum of about 200 mg. a day at the beginning, but the level usually dropped to about 150 mg. by six weeks. Counting 280 mg. a day intake with 20 mg. lost in sweat, feces and sputum, it leaves a consumption of from 60 to 150 mg. a day. A few very ill patients had a high value of only 150 mg. in the urine and a gradual drop to 120 or less as the winter came on, making a consumption of 110 mg. at the beginning and rising to 140 mg. at the end of the test period. This reveals that severe cases require approximately 150 mg. or more a day to care for their needs (chart 3).

THE THIRD MASS THERAPEUTIC EXPERIMENT

The result of the third mass experiment, in which 63 cases were selected (29 of which were followed for more than a year) was comparable to the other two.

SUMMARY AND CONCLUSIONS

An extensive study of the vitamin C economy in tuberculosis was undertaken. This work included 79 tuberculous patients in studies on saturation and 282 in the treatment of the disease, of which 128 were studied for more than one year. The organs of thirty-two bodies in which death occurred from various diseases (mostly tuberculosis) were analyzed for vitamin C. Many other analyses were performed on sputum, urine and blood.

In moderately or early far advanced cases there is only a slight unsaturation of vitamin C after ten to twelve days of a basic diet of approximately 31 mg. a day.

In the more advanced cases there were varying degrees of "exhaustion" of vitamin C appearing to be proportional to the severity of the disease and the intake of vitamin C. The speed of "exhaustion" was several times more rapid in the more severely diseased than normal. There is an "unaccountable" quantity ranging up to 150 mg. a day, most of which is diverted by severe tuberculosis. In one terminal case 60 per cent of the vitamin C administered was unaccounted for. Critically ill patients may reach a level as low as 0.3 mg. per hundred cubic centimeters of blood and 6 to 10 mg. per twenty-four hours of urine. It is estimated that in such low levels not more than 300 mg. is present in the body.

Patients on peptic ulcer diets, nonresidue (diets for enteritis), patients following massive operations and alcoholic addicts are prone to become unsaturated with vitamin C.

Special diets high in vitamin C will prevent or relieve the unsaturation, but on rare occasions (such as in peptic ulcers) it may be more suitable to supply the vitamin C by intravenous injection of a salt of ascorbic acid.

The observations justify the tentative recommendation that no patient should have less than the optimum standard dosage of 0.84 mg. per kilogram of body weight a day (50 to 60 mg. total) and that the quantity of the vitamin should be increased to 200 mg. a day progressively with the severity, activity and duration of the disease.

It was found that in saturation there was roughly 5 mg. of vitamin C per hundred grams of total body tissue, which would represent a total quantity of 3 to 5 Gm. in the normal body. Without supplementary administration of vitamin C this quantity is dissipated in advanced tuberculosis before death, sometimes to a negligible quantity.

The vitamin C seems to exist in increasing concentration in proportion to the vitality of the cells. It is highest in the hypophysis, gonads, adrenals, pancreas and thyroid. There is a rather high level maintained in the liver and brain even in severe depletion, so that in an extreme degree of unsaturation these organs, because of their size as well as of a relatively high concentration, may contain as much as three fourths of the body supply. Muscle, fat and bone are low in vitamin C but because of their volume constitute large depots during health.

There is a slight hematinic effect in treated patients as compared to controls during the first few months of treatment, but the favorable effect seemed to disappear between six to nine months' time.

Frequently, when the disease is far advanced, patients deficient in vitamin C are benefited by being kept saturated with the vitamin, as shown by a prolongation of life of the treated patients over the controls, as well as slightly more favorable clinical and laboratory observations. Adequate vitamin C is therefore just one of the many factors necessary for a proper treatment of tuberculosis.

No benefit was noted in an excess beyond saturation.

EFFECTIVE TEMPERATURE SCALE

A MEASURE OF HUMAN COMFORT IN ENVIRONMENTAL TEMPERATURE

MURRAY B. FERDERBER, M.D.
AND
F. C. HOUGHTEN, M.S.
PITTSBURGH

Maintenance of constant body temperature equilibrium over a wide variety of activities and environmental conditions constitutes one of the most important problems in the physiology of life. Normal temperature is maintained through a balance between heat production by metabolism and heat loss to the surroundings. The mechanism of metabolism and its control is well understood by the physiologist.

There are four factors in the atmospheric environment which affect heat loss from the body and, therefore, this equilibrium. They are (1) the temperature of the air, (2) its moisture content, (3) air movement and (4) radiation transfer between the body and surrounding surfaces. Generally speaking, these four factors are given in the order of their importance, and it is natural that what is known as the temperature of the air, better expressed as the dry bulb temperature, was the first of these values to be given consideration by the physiologists in the medical profession. However, with the growing advance in our knowledge of the relative value of these factors and the greater precision with which they may be observed and controlled, it is possible and desirable that our profession become familiar with these relationships and with their effect on human physiology. Since thermal equilibrium of the body in health and disease is important, the time has come when the physician should regard these environmental requisites more critically.

Through research carried on cooperatively during the past twenty years by physicians of the United States Public Health Service,[1] the United States Bureau of Mines [2] and the Research Laboratory of the American Society of Heating and Ventilating Engineers,[3] not only has the effects of these four environmental factors in controlling heat exchange between the body and the

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Dr. Ferderber is research fellow and Mr. Houghten is associate fellow, Department of Industrial Hygiene, University of Pittsburgh School of Medicine, and research director, American Society of Heating and Ventilating Engineers.

1. Sayers, R. R., and Davenport, S. J.: Review of Literature on the Physiological Effects of Abnormal Temperatures and Humidities, Pub. Health Rep. **42**: 933 (April 8) 1927.
2. Houghten, F. C.; Yagloglou, C. P., and Sayers, R. R.: Effective Temperatures for Still Air Conditions and Their Application to Mining, Bureau of Mines Reports of Investigations, Serial No. 2563, Jan. 1924.
3. McConnell, W. J., and Houghten, F. C.: Some Physiological Reactions to High Temperatures and Humidities, Tr. Am. Soc. Heat. & Ventil. Engin. **29**, 1923.

atmosphere been evaluated but these factors have been combined into a single comfort index known as the effective temperature.[4] This scale takes into account the temperature of air, its moisture content and movement. It has been shown that this effective temperature index, particularly in hot atmospheres, is a true measure not only of a person's feeling of warmth but of many of his physiologic reactions including changes in body temperature, increase in pulse rate and change in leukocyte count of the blood.

The psychrometric chart shows the thermal dynamic relationships between the moisture content and the temperature of the air, including therein a series of equal feeling of warmth lines as affected by these factors, known as the effective temperature lines. This chart is for still air. The additional factors of air movement and radiation between the body and surrounding surfaces may be similarly shown on other charts. However, since the latter are of relatively little importance for normal living conditions, their effect need be taken into consideration only in rare cases in which high air velocities and excessive radiation are encountered.[5] A consideration of the combined effect of temperature and humidity of the atmospheres in the effective temperature index requires not only an ordinary thermometer, or dry bulb, but also a wet bulb, which is a thermometer having a wetted wick around the sensitive element. These two instruments are combined into a sling psychrometer which gives the dry and wet bulb temperatures of the air. For most satisfactory usage this combined instrument should be affected by rapid air movement, which in the original instrument was obtained by whirling or slinging the instrument around in a circle at the end of a chain or rod with a suitable handle and swivel. The modern instrument utilizes either a fan or an atomizing bulb to produce the necessary air movement over the wet bulb. When properly used, the wet bulb temperature is usually below that of the dry instrument. The wet bulb reading for any air condition, therefore, is the lowest temperature which may be realized by a wetted surface due to heat loss by evaporation. For example, on a moderate summer day when the moisture content or relative humidity is low the dry bulb and wet bulb temperatures as determined by the sling psychrometer may be 90 F. and 67 F., illustrated as point *A* on chart 1, while on a summer day when the relative humidity is high the dry bulb and wet bulb temperatures may be observed as 90 F. and 81.5 F. shown as point *B* on the chart. Reference to the chart shows condition A as a relative humidity of 30 per cent and an effective temperature of 78 F., while condition B is shown as a relative humidity of 70 per cent and an effective temperature of 84.5 F. Although both of these conditions show the same dry bulb temperatures as observed by an ordinary thermometer, condition B will be considerably warmer, as indicated by its high effective temperature, which is a combined index of the temperature and moisture content of the air affecting a person's feeling of warmth. The first condition with a moderately low air movement will give ideal comfort for a person who is seated at rest in the shade with normal summer clothing, while condition B with the same air movement will be too warm for comfort and will result in considerable perspiration.

It has been determined that an average American seated at rest in his living room, theater or other places of assemblage will be ideally comfortable at about 66 F. effective temperature during the winter season, but in a summer cooled space he would be ideally comfortable at about 72 F. As indicated by points *C* and *D* (chart 1), this may be observed with 75 F. dry bulb at 70 per cent relative humidity, or 80.5 F. dry bulb at 30 per cent relative humidity. Most people would be uncomfortably warm and perspiring at an 85 F. effective temperature irrespective of the moisture content-high dry bulb combination responsible for this condition. Most persons seated at rest will maintain temperature equilibrium with profuse perspiration in an effective temperature as high as 89 F. At higher effective temperatures body heat equilibrium will not be maintained; body temperature will rise and pulse rate will increase

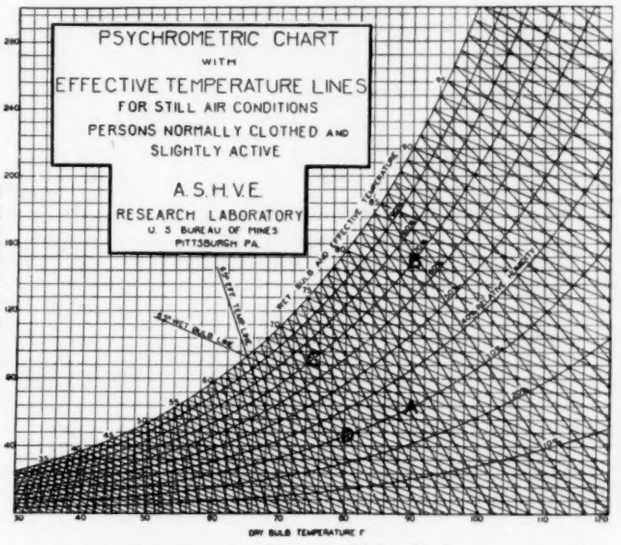

Chart 1.—Psychrometric chart for high effective temperatures.

as the effective temperature increases, so that in a condition of 92.5 F. effective temperature the average person will have a rise of 1.7 degrees Fahrenheit in body temperature and an increase in pulse rate of 48 per minute in three hours. The same physiologic changes will occur at an effective temperature of 96.5 F. and 20 per cent relative humidity when the dry bulb is 131 F., or 32 degrees Fahrenheit above body temperature, as would occur in 96.5 F. effective temperature with a high relative humidity of about 90 per cent when the dry bulb temperature is only 99 F., or approximately the same as the body temperature. It may be interesting to compare the condition of 99 F. dry bulb and 20 per cent relative humidity when the effective temperature is 81.8 F. with a condition of 135 F. dry bulb and 90 per cent relative humidity when the effective temperature is 121 F. In the first instance a human being will be comfortably warm and will have no temperature or pulse disturbance, but in the latter situation the condition is actually unbearable and increases in body temperature and pulse rate become violent. Therefore, at any point on the effective temperature lines the feeling of comfort and most of the physiologic changes will be the same irrespective of the changes in relative humidity or dry bulb.

4. Houghten, F. C., and Yagloglou, C. P.: Determining Lines of Equal Comfort, Tr. Am. Soc. Heat. & Ventil. Engin. **29:** 163, 1923; Cooling Effect on Human Beings by Various Air Velocities, ibid. **30:** 193, 1924.

5. McConnell, W. J.; Houghten, F. C., and Yagloglou, C. P.: Air Motion—High Temperatures and Various Humidities—Reactions on Human Beings, Tr. Am. Soc. Heat. & Ventil. Engin. **30,** 1924.

A tremendous amount of research has been conducted to evaluate the relative effects of atmospheric environments on water balance or dehydration of the body. Whether one is treating patients for diseases or is managing workers, these statements hold true, since the heat loss is based on physical laws which have already been described.

As previously pointed out, extensive research has shown that definite physiologic reactions follow the effective temperature index rather than the dry bulb temperature. This fact should be important in the treatment of many human illnesses in which temperature derangement is encountered. As an example, Simpson [6] has shown that induced fever therapy will give a rise in body temperature to 105 F. in from forty minutes to an hour with a dry bulb temperature ranging from 130 to 150 F. and a relative humidity from 35 to 50 per cent. However, Houghten, Ferderber and Gutberlet [7] have shown that in a saturated atmosphere the same rise in body temperature will occur in about the same time with a dry bulb at approximately 113 F. There are no arguments offered here in favor of either high temperature and low humidity or relatively low temperature and high humidity in obtaining the desired end, but it should be obvious that with this wide difference in results, depending on the moisture content of the air, a greater appreciation of these facts should be of value in the field of medicine.

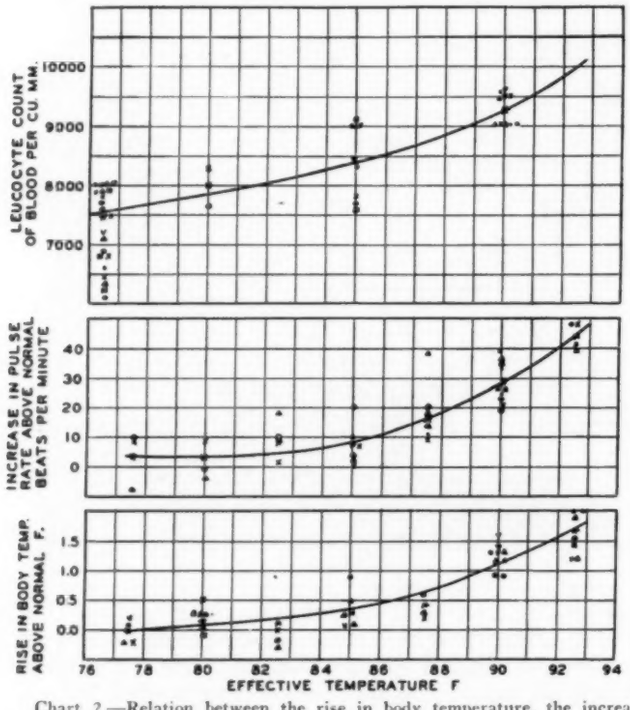

Chart 2.—Relation between the rise in body temperature, the increase in pulse rate, the change in the leukocyte count from normal during three hours' exposure and the effective temperature of the air condition.

Research during recent years by us has also served to show very wide differences in the mode of heat losses depending on the moisture content of the air.[8] In this connection we would point out that the human body loses heat essentially by contact with the air; that is, the air in contact with the human body absorbs heat and moves away, allowing cooler air to come in contact with the body. This is known as sensible heat loss. At the same time, dry air in contact with the human body, particularly when it is bathed in perspiration, evaporates moisture from the surface and thereby removes heat equal to the latent heat of evaporation of perspiration removed, or 575 large calories per gram. This is recognized as latent heat loss.

A normal-sized man 68 inches tall (173 cm.), weighing 150 pounds (68 Kg.) seated at rest normally clothed dissipates about 100.8 large calories (400 British thermal units) of heat per hour without much variation for all temperatures above 60 to 70 F. The division of these calories between sensible and latent depends on the moisture content and the temperature of the atmosphere. For example, at 65 F. effective temperature, which is reasonably comfortable for a person normally clothed and seated at rest in winter, this person dissipates a total of 100.8 large calories per hour. About three fourths of this is sensible and one fourth latent, while for an effective temperature of 75 F., which is slightly warm for a summer conditioned space, approximately 67.5 per cent of the total heat is sensible and 32.5 per cent is latent. At 85 F. effective temperature, which represents a very warm but not unbearable condition, he loses the same amount of heat, of which 42.5 per cent is sensible and 57.5 per cent is latent. If the dry bulb temperature is equal to the body temperature, the entire amount of heat dissipated is latent. The foregoing values are subject to some variation, depending on the relative humidity of the air. This variation for most conditions is not great. A better division of these values is given by Houghten and others.[9]

From a practical standpoint this application may well be utilized in measuring the effects on workers in industry in which all gradations of the temperature range may occur. The physiologic effects of high effective temperatures can be well illustrated by the increases in pulse rates, elevations of body temperatures and, lastly, a rise in leukocyte count of the blood.[10] Since we have shown that a rise in body temperature is a function of effective temperature, it is only natural that the pulse rate should follow the body rise. However, psychic stimuli definitely play a great part in changes in heart rate but can be disregarded after a period of adjustment to the hot environmental conditions. The change in leukocyte count may be more difficult to evaluate, since this observation was made incidental to the other data. Additional investigations by the authors show the rise in white cell count to be consistent in laboratory observations over the past two years, although no specific explanation is offered. Since much of this information was collected under conditions which might simulate certain unusual occupations, one could conclude that the physiologic changes may be caused by environment. It was observed in investigations on fever therapy by this department that frequent exposures to heat at short intervals produced a state of resistance to the heat itself and was accompanied by

6. Simpson, W. M.: Artificial Fever Therapy of Syphilis and Gonococcic Infections, Brit. J. Ven. Dis. **12**:133 (July) 1936.

7. Houghten, F. C.; Ferderber, M. B., and Gutberlet, Carl: Fever Induced by Conditioned Air, Tr. Am. Soc. Heat. & Ventil. Engin. (Sec. Heating, Piping & Air Conditioning), February 1937.

8. Houghten, F. C.; Teague, W. W.; Miller, W. E., and Yant, W. P.: Thermal Exchanges Between the Human Body and Its Atmospheric Environment, Am. J. Physiol. **88**: 386 (April) 1929; Thermal Exchanges Between the Bodies of Men Working and the Atmospheric Environment, Am. J. Hyg. **13**: 415 (March) 1931.

9. Houghten, F. C.; Teague, W. W.; Miller, W. E., and Yant, W. P.: Heat and Moisture Loss from the Human Body and Its Relation to Air Conditioning Problems, Tr. Am. Soc. Heat. & Ventil. Engin. **35**: 245, 1929; Heat and Moisture Losses from Men at Work and Their Application to Air Conditioning Problems, ibid. **37**: 541, 1931.

10. Fleisher, W. L.; Stacey, A. E., Jr.; Houghten, F. C., and Ferderber, M. B.: Air Conditioning in Industry, J. Am. Soc. Heat. & Ventil. Engin. **45**: (Jan.) 1939.

failure of leukocytosis at the same time.[11] While this holds true for certain chronic illnesses, a vague possibility exists that there is a connection between continued exposures to excessively hot atmospheres over a long period of time and resistance to infection.[12]

At an approximate effective temperature of 85 F., the changes in body temperature, pulse rate and leukocyte count become noticeable, so that an effective temperature between 92 and 94 F. the differences in these three physical readings from normal are rather extensive. It must be remembered that these changes occur in laboratory subjects performing light work standing whose metabolic output amounts to 76 calories per square meter per hour. One could conclude that, had these subjects been seated at rest, the physiologic changes would have been less significant or, had they been performing heavy work of about 150 calories per square meter per hour, the changes would have been greater. This is offered as a measure for evaluating the exposure time in new processes of manufacture, so that the medical managers have some definite conception of what changes occur in the body of the industrial worker.

We offer no definite point at which conditions may be considered unsafe, since this is purely experimental, and its application may be of some value in our vast industrial life[13] (chart 2).

There is some indication that at different seasons of the year physiologic reactions may vary according to the same effective temperatures. In a recently published paper[14] this is clearly indicated to be between 81 and 90 F. effective temperature; but in excessively hot atmospheres of approximately 92 F. effective temperature or higher the physiologic changes are the same, irrespective of the season of the year. We have called this circumstance "acclimatization," indicating that the physiologic responses become adjusted to environmental temperatures.

Since the use of air conditioning has been more critically evaluated, its application to human comfort will interest the physician irrespective of locality. It is desirable to know the optimum comfort in winter heating or summer cooling in different geographic locations, so that some conclusions could be drawn as to the proper conditions for comfortable living in certain regions.[15] These desires are interpreted in chart 3, in which occupants of certain spaces indicated their wishes regarding the comfort or discomfort of the conditions, all of which was plotted against the effective temperature in each location.

A rather interesting outcome of these collected data was the choice of the proper effective temperature to be used in an experimental operating and recovery room at the Elizabeth Steel Magee Hospital,[16] associated with the University of Pittsburgh. Of the many theories that have been advanced regarding the differences between inside and outside temperatures, we felt that an average of the comfort requirements in various localities would furnish some idea of the proper conditions. An effective temperature between 67 and 70 F. was chosen and the variation from these conditions was so slight that 80 per cent of the operating room personnel voted "comfortable," which coincided with the choice of office workers in other portions of the country. Apparently the surgeons desired a slightly cooler environment, owing perhaps to working while standing, the type of effort involved, heavier clothing and possibly mental stress. On the other hand, the office worker is usually seated, performs lighter work and wears less clothing. This does not mean, however, that the environment of the office workers is comfortable for the surgeon, but it does furnish a basis for scientific investigation of what the optimum environmental conditions might be.

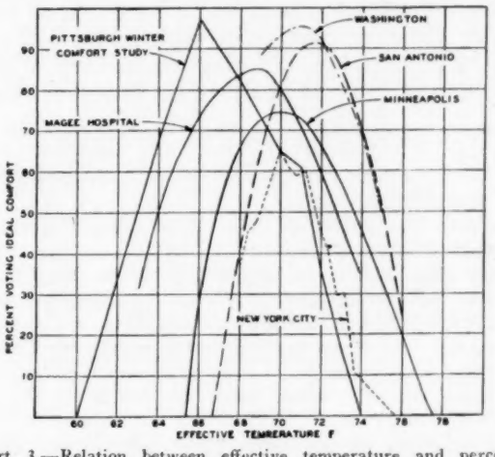

Chart 3.—Relation between effective temperature and percentage of persons indicating ideal comfort in various localities as indicated on graph.

ABSTRACT OF DISCUSSION

DR. W. J. MCCONNELL, New York: The authors have evaluated in the order of their importance the various physical factors of the air which determine in large measure the sensation of bodily comfort. Too much dependence cannot be placed on the dry bulb temperature. It is like reading the time by one hand of the clock. It gives considerable information but not complete information. In order to express similar sensations of comfort produced by thermally equivalent air conditions, the term "effective temperature index" was coined and need not be confusing if we remember first that effective temperature in reality is not a temperature at all, but merely a relative index of the temper of atmospheric conditions felt by the human body in response to the physical factors of the air. The scale is merely superimposed on the standard psychrometric chart. Second, we must consider that radiant heat is not included in the effective temperature. Where radiant heat sources prevail, they must be taken into consideration separately. Third, the index is based on saturation temperature; therefore the effective temperature index is usually lower than air temperature. Now, in order to improve that condition there is available a chart which has been revised on a 50 per cent relative humidity, so that the so-called comfort line is indicated by 70 rather than 66 and perhaps is better understandable by the majority of people who are accustomed to using the dry bulb temperature as an index for comfort.

11. Report of the Second Year of Fever Therapy Research, Department of Industrial Hygiene, School of Medicine, University of Pittsburgh, 1939.

12. Ferderber, M. B.: The Effect of Heat on the Temperature-White Cell County Relationship of the Body, Department of Industrial Hygiene Publication, to be released.

13. Houghten, F. C.; Ferderber, M. B., and Rosenberg, A. A.: Physiological Effects of Hot Atmospheres, Indust. Med. (Indust. Hyg. Sect.) **9**:7-17 (Jan.) 1940.

14. Houghten, F. C.; Rosenberg, A. A., and Ferderber, M. B.: Seasonal Variation in Reactions to Hot Atmospheres, J. Am. Soc. Heat. & Ventil. Engin. **46**, January 1940.

15. Newton, A. B.; Houghten, F. C.; Gutberlet, Carl, and Qualley, R. W.: Summer Cooling Requirements of Two Hundred and Seventy-Five Workers in an Air Conditioned Office, J. Am. Soc. Heat. & Ventil. Engin. **43**: 758 (Dec.) 1937. Tasker, C.: Cooling Requirements for Summer Comfort Air Conditioning in Toronto, ibid. **44**: 405 (June) 1938. Rummel, A. J.; Giesecke, F. E.; Badgett, W. H., and Moses, A. T.: Reactions of Office Workers to Air Conditioning in South Texas, ibid. **45**: 323 (May) 1939. Houghten, F. C.; Gutberlet, Carl, and Rosenberg, A. A.: Summer Cooling Requirements in Washington, D. C., and Other Metropolitan Districts, ibid. **45**: 387 (Sept.) 1939. McConnell, W. J., and Spiegelman, M.: Reactions of Seven Hundred and Forty-Five Clerks to Summer Air Conditioning, ibid. Sect. Heating, Piping & Air Conditioning **46**: 317-322 (May) 1940.

16. Houghten, F. C., and Cook, W. L., Jr.: Air Conditioning Requirements of an Operating Room and Recovery Ward, J. Am. Soc. Heat. & Ventil. Engin. **45**: (Jan.) 1939.

LEUKOPENIA

A DISCUSSION OF ITS VARIOUS MODES OF PRODUCTION

JOHN S. LAWRENCE, M.D.
ROCHESTER, N. Y.

It has seemed to me that the average clinician spends little time in considering what physiologic mechanism may be at fault in patients who have leukopenia. One is prone to explain the condition on the basis of some abnormality in production of white blood cells by the hemopoietic tissue. While it is true that leukopenia is due in many instances to the failure of the blood-forming tissues to manufacture normal numbers of white blood cells, yet there are at least four other major mechanisms which may result in this condition. My purpose in making this presentation is to call attention to these additional conditions in the hope that all physicians may put more thought on leukopenia. With this in mind I present the following possibilities which I feel may take part in the development of leukopenia:

1. Diminished manufacture of white blood cells. This may be the result of (1) simple inhibition, (2) maturation arrest, (3) aplasia of the bone marrow and (4) infiltration of the bone marrow with foreign cells.

2. Increased elimination of white blood cells. Theoretically, this may occur when large quantities of cells are poured into an infected area such as an empyema or when large numbers of cells are lost through normal channels such as the gastro-intestinal tract, the lungs, the spleen or the liver.

3. Increased rate of destruction in the peripheral blood due either to abnormal white blood cells or to abnormal substances in the blood channels which cause destruction of the white blood cells.

4. Redistribution of the white blood cells in the vascular channels, such as occurs with foreign proteins.

5. Redistribution of the white blood cells in the body as a whole, as is seen at times in leukopenic phases of leukemia.

DIMINISHED MANUFACTURE OF WHITE BLOOD CELLS

With regard to diminished manufacture of white blood cells, this may occur under the following conditions:

1. *Simple Inhibition.*—Such is thought to occur in many of the virus infections, typhoid, malaria and overwhelming infections. No satisfactory study has yet been made of these disorders in relation to the cause of leukopenia, and it is probable that other mechanisms, such as peripheral destruction, are at fault. The fact that a "shift to the left" is frequently present suggests that increased destruction or elimination may be factors also.

2. *Maturation Arrest.*—This is a term which was first proposed by Fitz-Hugh and Krumbhaar.[1] These investigators called attention to the fact that extreme leukopenia occurred at times in acute agranulocytosis of the Schultz type when aplasia of the granulocytic elements of the bone marrow was not present but, on the other hand, when myeloblasts or myelocytes or both were present in normal or increased numbers in the bone marrow. An analogy was drawn between this situation and that existing in primary anemia in which large numbers of parent red blood cells were to be found in the bone marrow in the presence of few adult red blood cells in the peripheral blood. According to Fitz-Hugh and Krumbhaar,[1] the leukopenia in cases of acute agranulocytosis presenting normal numbers of parent white blood cells in the hemopoietic tissues was due to maturation arrest or failure of the white blood cell progenitors to maturate into late myeloid forms. Plum,[2] in a discussion of this entire subject, has pointed out that in the majority of instances acute agranulocytosis is associated with aplasia of the granulocytic elements of the bone marrow. However, he has shown that in an appreciable number of instances this disease may occur in the presence of pathologic changes of the type reported by Fitz-Hugh and Krumbhaar.[1] The fact has been stressed that there is unanimity of opinion as to the absence of differentiation of the myeloid cells of the bone marrow in the active stages of the disease. According to Plum,[2] the differences in the condition of the bone marrow are to be explained by the different stages of the disease at which the bone marrow has been removed. He has postulated three stages of the disease as regards the bone marrow: one in which the bone marrow is poor in cells; another when the marrow is rich in cells or, in other words, when regeneration has begun but has not advanced to the stage of differentiation into late myeloid forms, and a third when the marrow picture is normal, which is to be found in patients who die from complications subsequent to

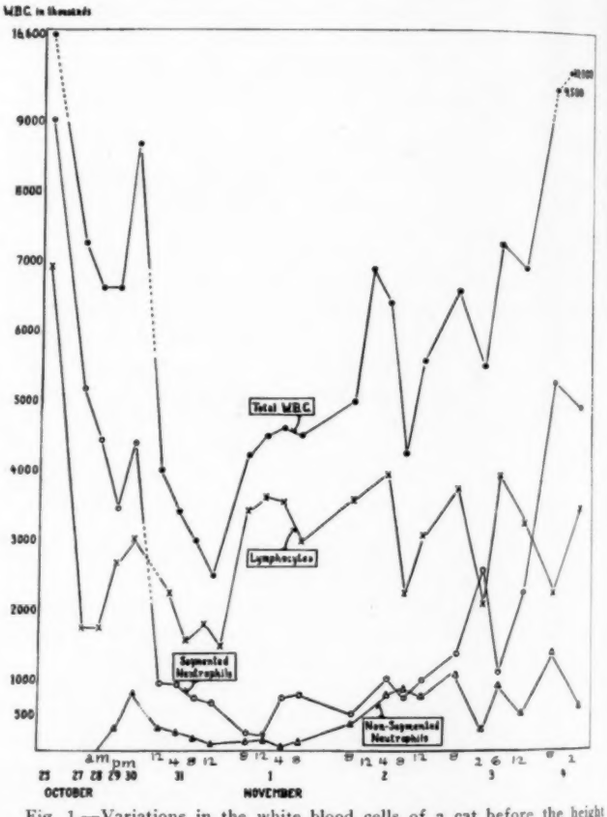

Fig. 1.—Variations in the white blood cells of a cat before the height of the disease, at the height of the disease and during the first days of recovery. Note the tremendous diminution in the neutrophils at the height of the disease and the increase in the stab forms just before the height of the disease and particularly during recovery. The lymphocytes are depressed, but not so markedly.

The expenses of this work were defrayed in part by a grant from the John and Mary R. Markle Foundation.

Read before the Section on Practice of Medicine at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

From the Medical Department of the University of Rochester School of Medicine and Dentistry and the Strong Memorial and Rochester Municipal Hospitals.

1. Fitz-Hugh, Thomas, Jr., and Krumbhaar, E. B.: Myeloid Cell Hyperplasia of the Bone Marrow in Agranulocytic Angina, Am. J. M. Sc. **183**: 104 (Jan.) 1932.

2. Plum, Preben: Clinical and Experimental Investigations in Agranulocytosis with Special Reference to the Etiology, London, H. K. Lewis & Company, Ltd., 1937.

hematologic recovery. Rohr [3] had presented his observations previously which were consistent with Plum's ideas in this regard. My associates and I [4] have shown

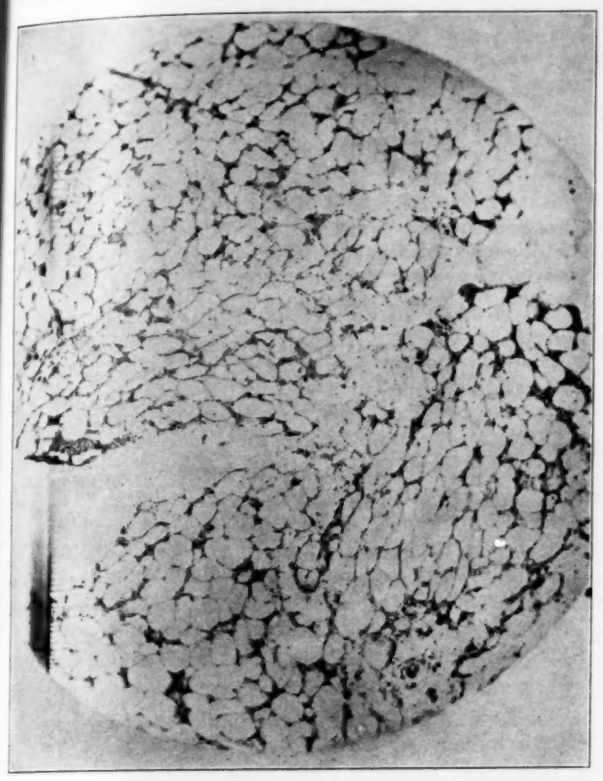

Fig. 2.—Section of bone marrow from femur of cat 279 at the height of the disease. Note the hypoplasia. Reduced from a photomicrograph with a magnification of 100 diameters.

recently that very rapid changes may occur in the bone marrow of cats with a disease which closely simulates the human disorder and to which we have given the name "infectious feline agranulocytosis." This disease was shown to be due to a virus or filtrable agent and was characterized by the development of leukopenia and pronounced neutropenia on the sixth to the ninth day after exposure to the infectious agent. There was no anemia of any note. Figure 1 shows the changes which occur in the white blood cells in a typical animal with this disease.

The pathologic changes were limited almost entirely to the bone marrow, lymph nodes, spleen and intestine. The changes in the lymph nodes and spleen were principally those due to proliferation of the reticuloendothelial cells. Intranuclear inclusion bodies were found in the epithelial cells of the gastrointestinal mucosa, in reticular cells of the lymphoid tissue and in the alveolar epithelium of the bronchial mucous glands. In the bone marrow, the most striking change was in the granulocytic cells. These were in most instances reduced in total numbers, and in all instances there was absence of differentiation into late myeloid forms at the height of the disease. The erythroid cells remained in normal percentages, and the same was true for the megakaryocytes. If the animal recovered, the bone marrow showed a very sudden and dramatic transformation. Within twenty-four hours the total number of bone marrow cells increased a great deal and, along with this, there was some differentiation into late myeloid forms. By the end of four days, the marrow had returned to an essentially normal picture. Figures 2, 3, 4, 5, 6 and 7 are typical areas of the bone marrow of one animal taken at the height of the disease and at twenty-four hours and seventy-two hours after recovery began. It will be seen from these illustrations that the bone marrow picture obtained in this disease varied a great deal, depending on the stage of the disease at which the specimen was obtained. If changes occur as rapidly in the bone marrow of the human disease as they do in that of the cat, it is easy to understand how various pictures may be ascribed to the bone marrow in the human disorder.

While it is conceded by all that maturation arrest and hypoplasia of the myeloid elements of the bone marrow probably represent the major processes involved in the development of neutropenia in cases of acute agranulocytosis, nevertheless it should be mentioned that, in the minds of some, these mechanisms do not explain the entire picture. Thus the sudden precipitous disappearance of neutrophils in patients sensitive to aminopyrine is difficult to explain on this basis, since the neutrophils may disappear from the peripheral blood within a few hours after the ingestion of aminopyrine. Fitz-Hugh [5] has suggested that peripheral destruction of the white blood cells may account for this part of the reaction in man. Recent studies at the University of Rochester point rather strongly to peripheral destruction being an important factor in "infectious feline agranulocytosis." Cats with severe leukopenia have had about one third of their blood removed by cardiac puncture at the same time that an equivalent amount of blood from a normal cat was being given into the femoral vein. By this procedure it has been found impossible to elevate the white blood cell count of the

Fig. 3.—Same section shown in figure 2, slightly reduced from a photomicrograph with a magnification of 1,500 diameters. Note the absence of differentiation of the myeloid cells.

leukopenic animal for more than a very brief temporary period. In another experiment, an animal with only 50 white blood cells per cubic millimeter was joined to

3. Rohr, Karl: Blut- und Knochenmarksmorphologie der Agranulocytosen, (Ergebnisse fortlaufender Sternalmarkuntersuchungen), Folia haemat. **55**: 305, 1936.

4. Lawrence, J. S.; Syverton, J. T.; Shaw, J. S., and Smith, F. P.: Infectious Feline Agranulocytosis, Am. J. Path. **16**: 333 (May) 1940.

5. Fitz-Hugh, Thomas, Jr.: Sensitivity Reactions of the Blood and the Bone Marrow to Certain Drugs, J. A. M. A. **111**: 1643 (Oct. 29) 1938.

a normal cat by means of the carotid arteries. Cross circulation was instituted and the animals lived for four hours. The total number of white blood cells was increased in the diseased animal to values comparable

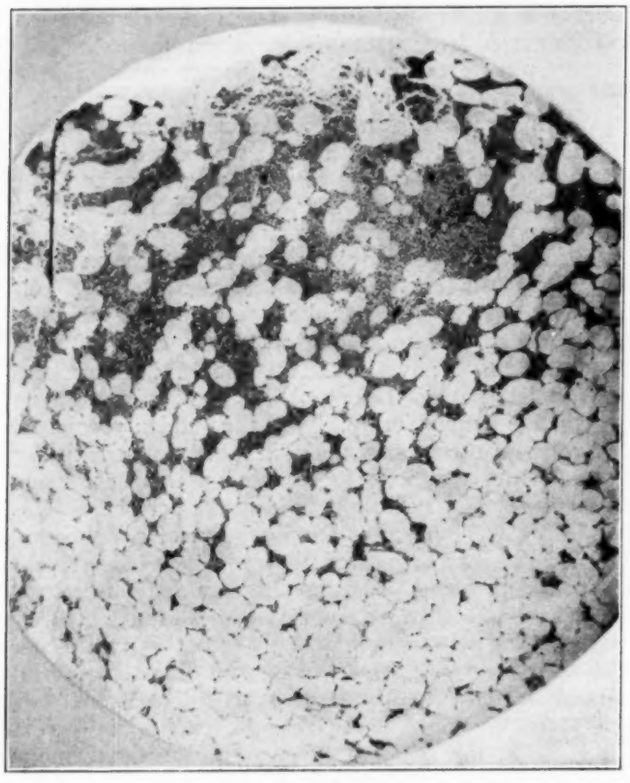

Fig. 4.—Section of bone marrow from femur of cat 279 on first day of recovery. The total number of cells has increased materially. Reduced from a photomicrograph with a magnification of 100 diameters.

with those for the normal animal, but there was a decided increase in early or "stab" forms, indicating that the bone marrow of the normal cat was being forced to work hard in order to keep the cells up to this level. A similar experiment with two normal cats did not result in any "shift to the left" during a period of twelve hours.

The following case is illustrative of leukopenia due to acute agranulocytosis:

CASE 1.—A. K., a white woman aged 76, a widow, was admitted to the Rochester Municipal Hospital April 12, 1935. The pathologic changes of interest were moderate pyrexia associated with a diffusely red throat and infection of the gums. She had a white blood cell count of 1,420 per cubic millimeter, all of which cells were lymphocytes. The red blood cell count was 3,500,000 per cubic millimeter, and the hemoglobin was 10.2 Gm. per hundred cubic centimeters. She died on the fourth day after admission, her white blood cell count having dropped in the interim to 200 per cubic millimeter. No neutrophils were found. The bone marrow of this patient showed moderate depletion of myeloid cells, all of which were of an early undifferentiated type. Red cell progenitors were in normal abundance. Figure 8 shows a typical area from a stained section of this bone marrow.

3. *Aplasia of the Bone Marrow.*—Not many cases of true pathologic aplasia of the bone marrow are encountered, since most patients with so-called aplasia of the bone marrow have merely functional aplasia, as pointed out by Thompson and his associates.[6] As representative of true aplasia of the bone marrow may be mentioned the following case:

CASE 2.—F. G., a white man aged 56, married, was admitted to the Strong Memorial Hospital May 29, 1931 with the following blood picture: red blood cells 1,270,000 per cubic millimeter, hemoglobin 3.5 Gm. per hundred cubic centimeters, white blood cell count 3,600 per cubic millimeter. The differential white blood cell count was neutrophils 38 per cent, lymphocytes 58 per cent and monocytes 4 per cent. One normoblast was found in the blood smear. Platelets were practically absent from the blood smear. The patient died July 24, at which time the white blood cell count was 1,600 per cubic millimeter. The bone marrow showed marked depletion of cells of all types. Figure 9 represents a typical area from a stained section of the vertebral bone marrow of this patient.

4. *Infiltration of the Bone Marrow.*—This usually results in an increased number of white blood cells in the peripheral blood, but in exceptional instances, when the infiltration is marked, leukopenia may result.

INCREASED ELIMINATION OF WHITE BLOOD CELLS

A clear-cut illustration of this mechanism is not easy but theoretically it is a distinct possibility. In cases of severe infection, leukopenia occasionally results. The usual explanation of this is that the toxin or toxins elaborated suppress the bone marrow. However, there is no positive evidence that the leukopenia is due to this, and it may be that it results from massive loss of cells. The following case may be used for purposes of discussing this mechanism:

CASE 3.—E. J., a white woman aged 44, married, admitted to the Strong Memorial Hospital Dec. 26, 1934, had had diarrhea for four weeks and had a typical course of ulcerative colitis. Her white blood cell count was 2,050 per cubic millimeter and the differential picture was as follows: myelocytes 1 per cent, juveniles 7 per cent, stab cells 32 per cent, segmented cells 44 per cent, lymphocytes 16 per cent. At autopsy, multiple ulcers of the large intestine were found with acute inflammation and necrosis and multiple perforations of the cecum. The bone marrow showed large numbers of cells of

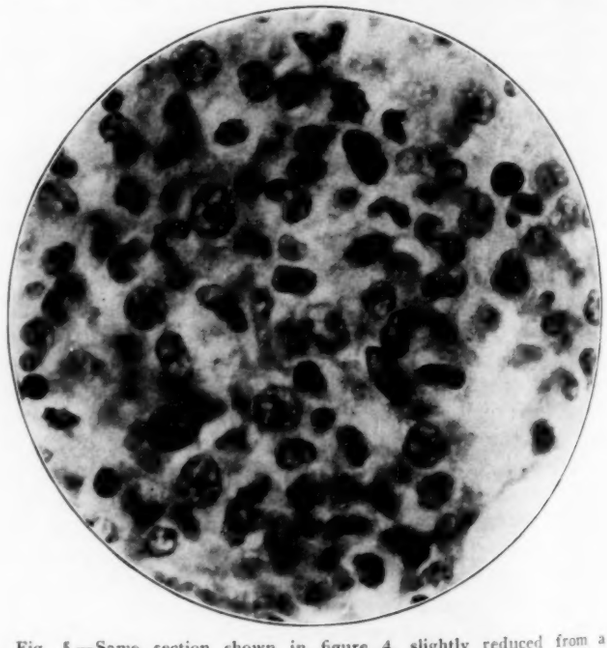

Fig. 5.—Same section shown in figure 4, slightly reduced from a photomicrograph with a magnification of 1,500 diameters. Note that differentiation of myeloid cells into stab forms is seen to have begun.

all types. There was a moderate increase in the number of eosinophils. The erythroid cells appeared normal. The myeloid cells were present in large numbers and showed good differentiation into adult forms. The megakaryocytes were normal.

6. Thompson, W. P.; Richter, M. N., and Edsall, Katherine S.: An Analysis of So-Called Aplastic Anemia, Am. J. M. Sc. **187**: 1 (Jan.) 1935.

It is obvious that several factors may have been responsible for the leukopenia. For example, poor absorption from the gastrointestinal tract, deficient food intake, elaboration of a leukotoxic substance and loss of white blood cells into the gastrointestinal tract or the peritoneal cavity or both should all be considered with reference to the leukopenia. However, we have had a few other cases of infection of the bowel associated with leukopenia, and it seems at least possible that the leukopenia may be due in part to increased elimination of white blood cells. Certainly the appearance of the bone marrow in this case points to satisfactory manufacture of these cells.

INCREASED RATE OF DESTRUCTION IN THE PERIPHERAL BLOOD

This could be due eiher to abnormality of the white blood cells or to abnormal substances in the blood

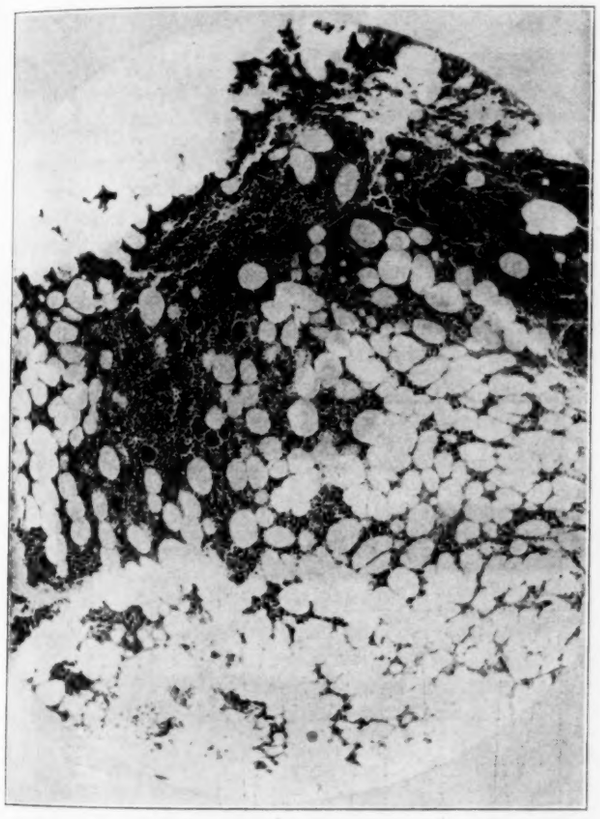

Fig. 6.—Section of bone marrow from humerus of cat 279 on the third day of recovery. Reduced from a photomicrograph with a magnification of 100 diameters.

plasma. I feel confident that both conditions exist at times. The following unusual case may be taken as illustrative of probable increased rate of destruction in the peripheral blood:

CASE 4.—W. G., a white woman aged 60, unmarried, has been seen in the Rochester Municipal Hospital on repeated occasions since 1928, the last admission being on Jan. 1, 1940. In 1928 she was found to have a white blood cell count of from 600 to 1,300 per cubic millimeter. On each of her admissions since then she has been found to have a pronounced leukopenia. Her admission in October 1939 was occasioned by excessive bleeding associated with thrombopenia, which she had not had previously. The differential count at this time was eosinophils 6 per cent, myeloblasts 1 per cent, myelocytes 10 per cent, juveniles 19 per cent, stab cells 7 per cent, segmented cells 11 per cent, lymphocytes 31 per cent, monocytes 10 per cent, degenerated cells 4 per cent, unclassified 1 per cent. The total white blood cell count was 1,700 per cubic millimeter. A specimen of sternal bone marrow revealed conditions within normal limits. In view of this and of the fact that this woman

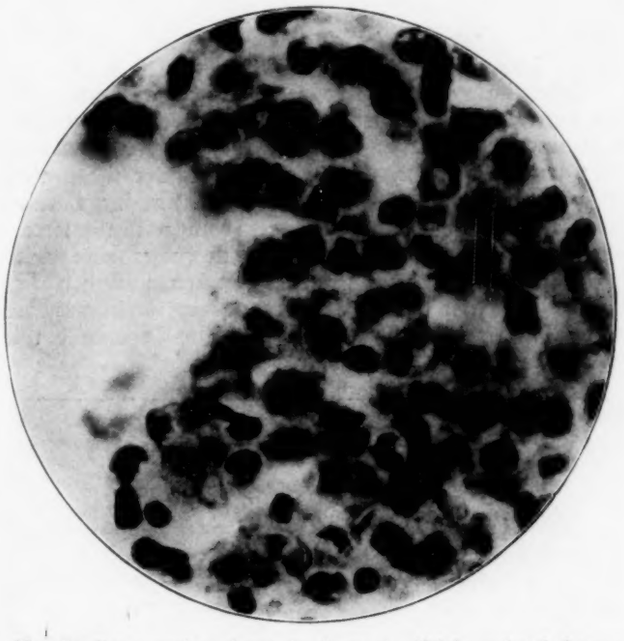

Fig. 7.—Same section shown in figure 6, slightly reduced from a photomicrograph with a magnification of 1,500 diameters. Note that normal differentiation of the myeloid cells was found.

had had severe leukopenia over a period of twelve years without any story of repeated or severe infections, it was felt that she probably was manufacturing a normal number of white

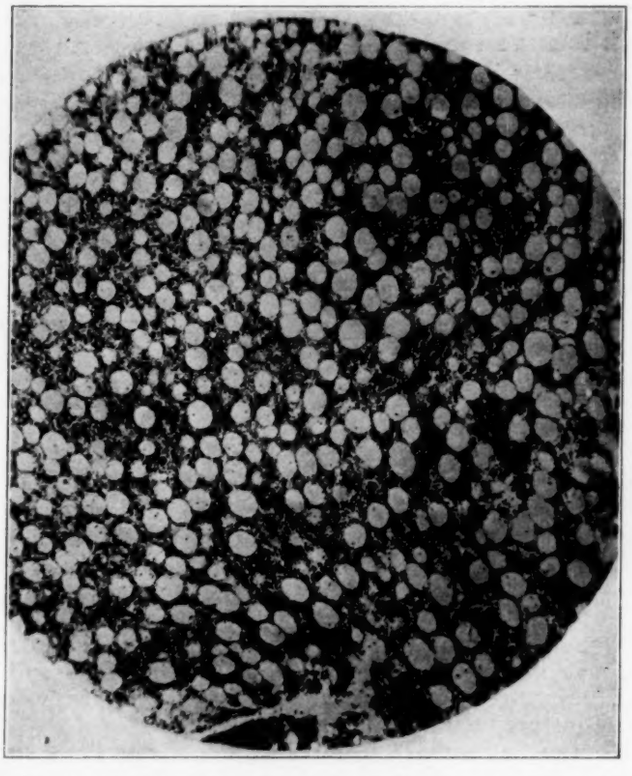

Fig. 8 (case 1).—Bone marrow in human acute agranulocytosis. Section of the vertebral bone marrow, reduced from a photomicrograph with a magnification of 100 diameters. Under high magnification, absence of differentiation of the myeloid cells was found.

blood cells. Her main difficulty seemed to be due to thrombopenia. Accordingly, it was decided to remove her spleen. This was done on January 22. Five hours after splenectomy she

had 13,000 white blood cells per cubic millimeter, and the differential count was juveniles 1 per cent, stab cells 34 per cent, segmented cells 53 per cent, lymphocytes 3 per cent, monocytes 7 per cent, degenerated cells 2 per cent. The white blood cell count gradually returned to its low level. She made an uneventful recovery and left the hospital free from hemorrhagic tendencies.

While the postoperative rise in white blood cells was not as severe as usual, it was appreciable, particularly since the normal level for this woman was low. This demonstrates that she was able, under the proper stimulus, to produce white blood cells in large numbers. The fact that she has gone so long with the leukopenia and without having any more trouble with infections than is customary for the normal adult makes me believe that she may have been manufacturing normal numbers of white blood cells. Of course this view is hypothetic and not proved.

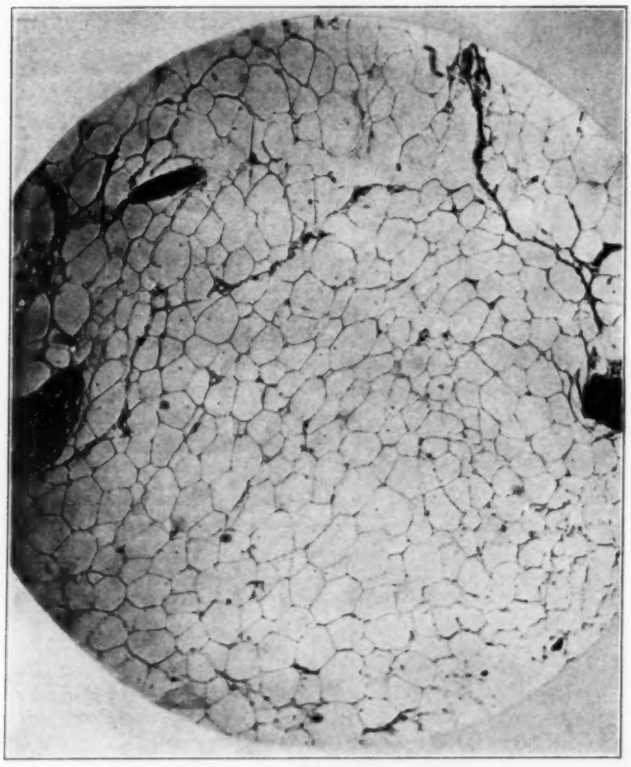

Fig. 9 (case 2).—Bone marrow in true aplastic anemia. Section of the vertebral marrow, reduced from a photomicrograph with a magnification of 100 diameters. Note the almost complete absence of cells of all types.

That white blood cells may be destroyed in large numbers in the peripheral blood has been shown conclusively by Chew, Stephens and Lawrence,[7] who were able to cause the disappearance of all neutrophils from the peripheral blood of the guinea pig in three minutes by the intracardial injection of antineutrophilic serum. This antiserum was produced by repeated injections of large numbers of neutrophils of the guinea pig into the ear vein of rabbits. Figures 10 and 11 show the effect of antineutrophilic serum on the peripheral white blood cell picture of the guinea pig. It will be seen that the effect of this antiserum on the neutrophils persisted for from twenty-four to eighty-four hours. Study of sections made from various organs of the body failed to reveal any accumulation of these cells in them. Further, it was shown that neutrophils could not be called forth by infection or other agents that ordinarily produced local accumulation of neutrophils in those animals which had been treated with antineutrophilic serum. For example, animals made leukopenic by the injection of this antiserum showed no accumulation of neutrophils

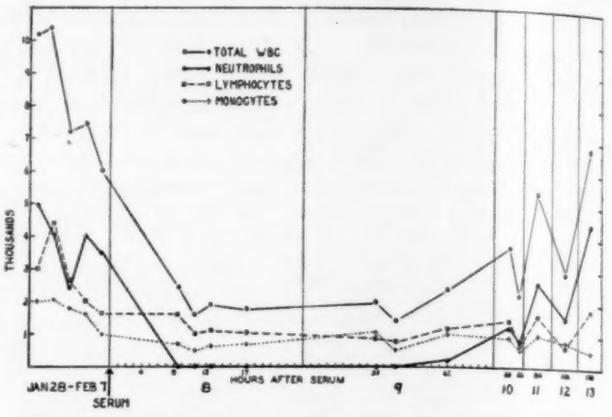

Fig. 10.—Effect of antineutrophilic serum on the peripheral white blood cell picture of the guinea pig. Note the decided drop in the number of neutrophils. These cells did not return to their normal level until eighty-four hours later.

in the subcutaneous tissue at the site of the injection of 0.1 cc. of a twenty-four hour broth culture of Staphylococcus aureus as contrasted with the local accumulation of large numbers of neutrophils in untreated healthy control animals when injected with the same amount of the broth culture. Recently, my associates and I have been able to show that, coincident with the peripheral leukopenia, there is a diminution in the

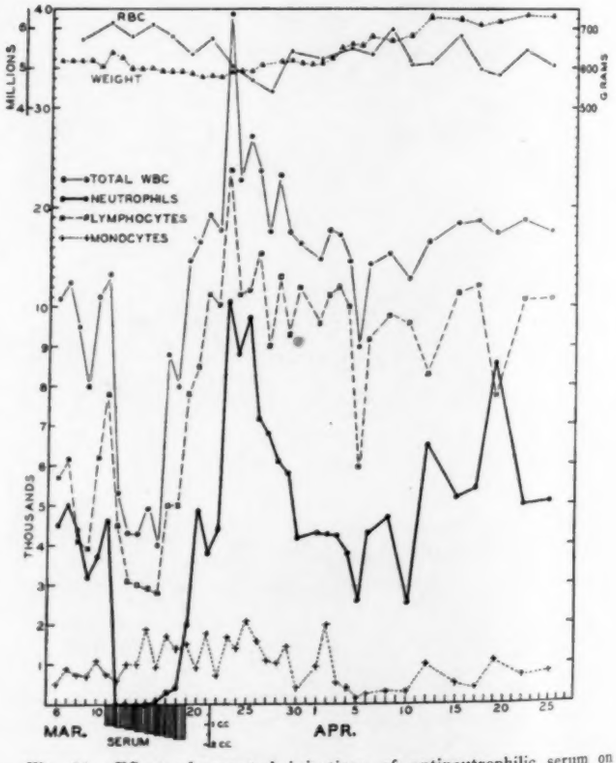

Fig. 11.—Effect of repeated injections of antineutrophilic serum on the peripheral white blood cell picture in the guinea pig. Note that the granulocytopenia was maintained for seven days and that there was a compensatory leukocytosis after this. The red blood cells were not affected.

number of white blood cells in the omental venules. This condition has been observed for three and one-half hours following intravenous injection and has been

7. Chew, W. B.; Stephens, D. J., and Lawrence, J. S.: Antileukocytic Serum, J. Immunol. **30**: 301 (April) 1936.

demonstrated in animals from twelve to eighteen hours after the intraperitoneal injection of antineutrophilic serum. In these studies we opened the peritoneal cavity of the guinea pig and removed a part of the intact omentum. This has been placed on a warm stage and kept moist with physiologic solution of sodium chloride. The circulation has been observed then through a microscope and, in some instances moving pictures have been taken.

REDISTRIBUTION IN THE VASCULAR CHANNELS

This is a well known phenomenon and has been commented on often in physiologic literature. One of the most detailed discussions of this subject with which I am familiar is that by Vejlens.[8] Hydrophile colloids such as gelatin, globulin and fibrinogen are known to produce peripheral leukopenia and neutropenia when given intravenously. This response is thought to be due to the white blood cells, particularly the neutrophils, assuming a marginal position in the venules in certain of the internal organs, i. e. liver, lungs, spleen and

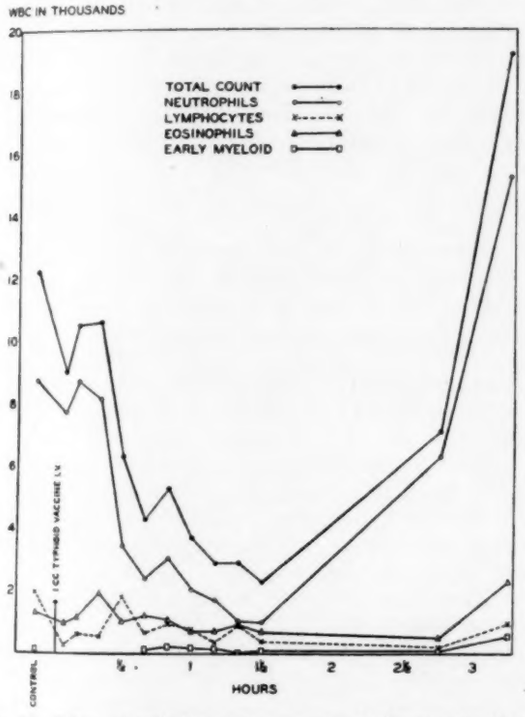

Fig. 12.—Effect of typhoid vaccine on the peripheral white blood cell picture of the cat; 1 cc. of typhoid vaccine was given intravenously.

omentum. This phenomenon can be readily observed under the microscope. My associates and I [9] have recently shown kodachrome moving pictures of the omental circulation which illustrate this reaction very well. One of the best clinical illustrations of this is to be found following injection of typhoid vaccine intravenously in man. Figure 12 shows the changes in the peripheral blood of the cat following injection of typhoid vaccine intravenously.

REDISTRIBUTION IN THE BODY AS A WHOLE

The mechanism that is responsible for the distribution of the white blood cells between the tissues and the vascular channels is unknown. However, under most conditions it functions well and maintains a normal ratio of cells in the vascular channels to those in the tissues. Occasionally this mechanism breaks down and one may find great numbers of cells in the tissues but only a few in the blood. The best illustration of this I know is in so-called aleukemic leukemia. In this condition there may be leukopenia and yet the various tissues in the body may be filled up with white blood cells. That this may occur in other conditions is a distinct possibility.

CONCLUSION

There are at least five different mechanisms which may be responsible for leukopenia. If more thought is given to leukopenia with reference to the mechanism which may be at fault, progress in its interpretation and handling will be enhanced.

260 Crittenden Boulevard.

8. Vejlens, Gert: The Distribution of Leukocytes in the Vascular System, Acta path. et microbiol. Scandinav., 1938, supp. 33, p. 1.
9. Lawrence, J. S.; Stringfellow, Margaret B.; Ackart, R. J.; Bishop, F. W., and Ariel, Irving: Infectious Feline Agranulocytosis: Kodachrome Moving Picture Demonstration of the Circulation of the Omentum as Affected by Serum from a Cat with This Disease, J. Clin. Investigation, to be published.

ABSTRACT OF DISCUSSION

DR. RUSSELL L. HADEN, Cleveland: The problem of leukopenia from the clinical point of view concerns the polymorphonuclear cells almost entirely. For this reason the term granulopenia seems preferable. Few of us appreciate what is happening to the granular cells normally. Each cell lives only a short time—probably not over four days—so that five to ten billion new cells must be released from the marrow every day to make up for those destroyed. The number of granular cells which can be made by the marrow to supply normal needs is enormous. The granular cells have little function while in the circulation. Cells in a stained film of blood are en route from the marrow to the point of activity. Almost all the cases of granulopenia seen clinically belong to Dr. Lawrence's first group. In thinking of granular leukopenia one considers (1) whether the marrow tissue is deficient in quantity as it is in the leukopenia of aplastic anemia; (2) whether the marrow tissue is functioning normally; the function is qualitatively impaired with aminopyrine intoxication, so the cells do not mature normally; in the depression seen with Banti's disease there is a quantitative decrease in function, or (3) whether there is some mechanical barrier to the emergence of cells from the marrow. In leukopenic myeloid leukemia the hyperplastic marrow seems to keep the cells from leaving the marrow normally. Probably this mechanical factor plays a more important part in leukopenia than is ordinarily realized. In the last two years, we have studied in our hematology laboratory 22 cases in which the total white blood cell count was below 2,500. In 2 an infection and in 4 various drugs had produced leukopenia by depressing the marrow. In 13 cases, leukemia or other bone marrow disease was responsible for the leukopenia. I was unable to classify 3 cases as to etiology. I will review our cases again in the light of Dr. Lawrence's discussion and try to determine whether the other mechanisms responsible for producing leukopenia might be operative in our cases. It is possible, as he suggests, that the cells may be taken out of the circulation rapidly or be destroyed in the circulation. We are indebted to Dr. Lawrence for emphasizing the numerous ways in which leukopenia may be brought about.

DR. JOHN S. LAWRENCE, Rochester, N. Y.: We have found it impossible to increase, except temporarily, the white blood cell count of animals at the height of the disease by means of replacement of large amounts of diseased cats' blood by the blood of normal cats. Of course we recognize that this does not prove that the cells were destroyed. They may have been lodged in the blood vessels in various areas of the body. We are trying to prove this point, and one of the procedures that we are carrying out is the use of cross circulation between the normal animal and the animal that has, say, 50, 100 or 200 white blood cells in the peripheral blood. I think that by means of this we shall be able to answer the question. We have not done enough work in this connection to make any final statement, but, as far as it goes, it does indicate that in

this particular disease (which is not a disease of man, however) there is peripheral destruction taking place, and that normal cells given to a diseased cat will be destroyed rapidly. I am not sure that I would agree entirely with Dr. Haden about placing almost all of the cases of leukopenia that we have in group I, since I feel that if more study is made of leukopenia we shall be able to place more and more patients with leukopenia in other groups.

THE USE OF BISMUTH COMPOUNDS IN SYPHILOTHERAPY

EDMUND N. WALSH, M.D.
WHITING, IND.
AND
S. WILLIAM BECKER, M.D.
CHICAGO

In the past twelve years the treatment of all types of syphilis at the University of Chicago Clinics has been planned with the use of much more bismuth than has usually been considered as standard or optimum treatment. In this report we wish to evaluate the results of such treatment of early syphilis, asymptomatic neurosyphilis and tabes dorsalis over a ten year period and compare these results, as far as possible, with corresponding data from the Cooperative Clinical Group studies.

PRESENT DAY STATUS OF BISMUTH IN SYPHILOTHERAPY

Since Sazerac and Levaditi [1] in 1921 first popularized bismuth as an antisyphilitic drug, it has gone through much the same cycle as was previously traversed by the roentgen ray and arsphenamine and as we have recently seen carried out with sulfanilamide. There was first a period of overoptimism, especially on the part of some members of the French school who hailed bismuth compounds as superior to the arsphenamines if not in initial potency certainly on the grounds of lesser toxicity. Many new bismuth preparations were offered for use with little or no investigation as to their efficacy or toxic effects. Reports soon began to appear of accidents in the course of treatment, intoxications, sometimes with fatal results, and later, evidence that the therapeutic efficiency of the drug was not nearly as great as was at first thought. The next portion of the cycle, in which we still find ourselves as far as bismuth is concerned, is that of careful experimental study and clinical trial which will eventually determine its place in the treatment of syphilis.

The present day knowledge of bismuth as an antisyphilitic drug can be briefly summarized. Bismuth will cure experimental syphilis in animals; it causes sterilization of surface lesions, reversal of the Wassermann reaction and cure as shown by lymph node transfers. "Cures" have been reported in a certain percentage of patients with early syphilis who were treated with bismuth compounds alone.[2] At the hôpital Cochin in Paris, bismuth has been used to the exclusion of the arsenicals in all types of syphilis since 1921 with what the staff considers good results.[3] On the other hand, there are reports of clinical and serologic relapses in patients while they were under bismuth therapy.[4] In addition, the prophylactic use of bismuth, which at first seemed to offer such a potent weapon for the control of syphilis, has been condemned because it does not uniformly prevent infection.[5] Thus bismuth alone, while sufficient in some instances, cannot be relied on to cure syphilis.

An enormous amount of work has been done, chiefly in this country, during the past fifteen years on the pharmacology of bismuth preparations (Cole and Sollmann, Hanzlik, Kolmer, Klauder, Gruhzit). In general, the effectiveness of bismuth salts in syphilotherapy seems to be directly proportional to the amount of elemental bismuth which is available in an ionizable form in the body. This is dependent on the bismuth content of the compound, its physical properties (tissue solubility), the vehicle used and the amount administered. The spirocheticidal effect varies in different animals.[6] There is also probably some difference in behavior between the electronegative and electropositive forms, especially as regards penetration of the nervous system.[7] The recent work of Eagle [8] suggests that the mode of action of bismuth in syphilotherapy is a direct spirocheticidal effect rather than a secondary effect through the formation of a protein-bismuth complex, bismoxyl, postulated by Levaditi.[9]

A large part of the experimental work deals with absorption, excretion and toxicity of the various bismuth preparations. It was found early that bismuth compounds given intravenously were highly toxic and could not safely be used therapeutically.[10] The literally hundreds of compounds that have been advocated for intramuscular use can be classified roughly as follows: (1) tissue soluble, (2) water soluble, (3) water soluble suspended in oil, (4) oil soluble in oil and (5) insoluble suspended in oil. Their tissue solubility, which determines the rate of absorption, decreases in the order in which they are listed. The tissue-soluble salts are rapidly absorbed to give a relatively transient high concentration of bismuth in the blood as gaged by a rapid urinary excretion. The toxicity of these preparations is greater, and their chemotherapeutic index in some cases may be as low as one.[6]

On the other hand, the insoluble salts suspended in oil are absorbed very slowly, and with repeated doses there is a cumulative effect. The therapeutic index of these preparations may be as high as 166.[6] A certain variable proportion of the bismuth introduced into the body is not excreted at once but is retained by the various organs and eliminated gradually over a long period of time. This is exclusive of the bismuth depots which are formed at the sites of injection when any but the

This work was aided by a grant from the Kuppenheimer Foundation.

From the Section on Dermatology, School of Medicine of the Division of Biological Sciences, University of Chicago.

Read before the Section on Dermatology and Syphilology at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

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8. Eagle, Harry: Minimal Effective Concentration of Arsenical and Bismuth Compounds on T. Pallidum in Vitro in Relation to the Therapeutic Dose, Am. J. Syph., Gonor. & Ven. Dis. **23:** 310 (May) 1939.

9. Levaditi, cited by Stokes, J. H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1934, p. 243.

10. Klauder, J. V.: Intravenous Injections of Bismuth Compounds in the Treatment of Syphilis: Their Use Clinically and in Experimental Syphilis in Rabbits, Arch. Dermat. & Syph. **17:** 332 (March) 1928.

tissue-soluble salts are used. The greater portion of bismuth is excreted through the kidney and the remainder through the bowel. The relative proportion varies considerably with the preparation used but in general is about 9 to 1. All investigators have found essentially the same percentage distribution of the stored bismuth in the organs and tissues. Listed in order of decreasing percentage content, they are kidney, liver, bile, spleen, ileum, colon, lung, jejunum, brain and blood. The actual amount of bismuth in any one organ depends on the dosage, but the relative distribution is independent of the amount given.

As might be expected, since approximately 90 per cent is excreted through the kidney and since this organ shows the highest concentration of bismuth, it is the first to show toxic effects in the experimental administration of bismuth. According to Kolmer [6] the injury is primarily and essentially a nephrosis with maximum changes in the convoluted tubules. The pathologic changes are the same regardless of the type of compound used, and thus probably are caused by the bismuth itself. Recent autopsy studies [11] have been made on 15 patients who received intramuscular bismuth therapy. In 2 there was evidence that renal damage due to bismuth probably contributed to the patients' death. However, renal damage did not seem to be proportional to the concentration of bismuth in the kidney.

COMPLICATIONS FROM BISMUTH THERAPY

The complications occurring during treatment that have been attributed to bismuth are many but fortunately the majority are of little real importance. Beerman [12] collected twenty-three deaths from the administration of bismuth recorded in the literature up to 1932. Of these six followed intravenous administration or were due to embolism subsequent to accidental intravenous injection. Seventeen deaths were due to delayed toxic effects which included acute yellow atrophy of the liver, stomatitis, nephritis, hemorrhagic phenomena and granulocytopenia. Vigne [13] listed the relative frequency of intolerance to bismuth in 202 of 2,390 patients as follows: stomatitis, 72 per cent; bismuth grip, 10 per cent; local pain, 9 per cent; abscess, 3.3 per cent; cutaneous eruptions, 5 per cent; all other, 6 per cent.

These proportions would vary considerably depending on the type of patient, technic of administration and the preparation used. The most common are oral complications varying from the well known blue line to ulceration. The frequency of actual stomatitis has been found to be inversely proportional to the quality of the oral hygiene of the patient.[14]

Some degree of local pain at the site of injection is about as frequently complained of as the blue line on the gums but it is seldom severe. In many patients there develop localized areas of induration in the gluteal muscles where the injections are usually given. These are in most cases only mildly tender. Formation of abscesses and localized embolism from accidental intra-arterial injection are relatively rare, although a considerable number of cases have been reported.[15]

The cutaneous manifestations of bismuth "hypersensitiveness" most commonly take the form of a mildly exudative pityriasis rosea–like eruption. Herpes zoster, exfoliative dermatitis and hemorrhagic, urticarial and erythema multiforme-like lesions have also been attributed to bismuth.[16] Jaundice at times has apparently been caused by the drug.[17] However, after jaundice and most of the cutaneous eruptions the drug may be resumed without a recurrence of the complication.

Most reactions to bismuth therapy are avoidable. Proper oral hygiene, careful injection technic followed by massage over the site of injection and regular examination of the urine would eliminate a high percentage of bismuth accidents and complications.

COMBINED TREATMENT WITH THE ARSPHENAMINES AND BISMUTH COMPOUNDS

A combined treatment of syphilis with the arsphenamines and bismuth was, of course, considered and tried soon after bismuth was found to be of use in syphilotherapy. For the most part there were two directly opposed trends of thought on the subject: (1) Why risk giving the toxic arsenicals when bismuth will accomplish the same result with a sacrifice only of time? (French school) or (2) Why bother with a less effective drug like bismuth when the arsenicals will do the work more quickly and better? (German school). In general it was considered that the combined toxic effects of the two drugs would offset any advantage gained.

Wright [18] in 1927 was one of the first in this country to advocate the simultaneous administration of bismuth and the arsphenamines. Schamberg [19] urged the use of combined treatment, giving as the chief advantage that thereby the dosage of and the reactions caused by the arsphenamines could be reduced. Both authors reported satisfactory serologic and clinical results. Sézary [20] in 1930 stated, after nine years' experience, that mixed treatment gave better results, no increase in toxic effects and fewer neurorecurrences, and he had also noticed that when arsphenamine was given with bismuth fewer cases of stomatitis were seen.

Clausen, Tatum and Longly [21] have recently found evidence working with experimental rabbit syphilis that provides a scientific basis for combined treatment. They found that whereas the therapeutic effects of fractional doses of the arsphenamines and bismuth given together are mathematically additive this does not hold true for their toxic effects. Thus, giving three quarters of the minimal curative dose of bismuth plus one quarter the minimal curative dose of an arsphenamine, or vice versa, will cure rabbit syphilis; giving these same proportions as applied to minimal lethal doses of the drugs does not cause death.

The system of treatment used in the University of Chicago Clinics was devised by one of us (S. W. B.) following a study of the various methods used for the treatment of early syphilis at the Mayo Clinic.

11. Scholtz, J. R., and Chaney, A. L.: Studies on Tissue Concentration of Bismuth in Man, Am. J. Syph., Gonor. & Ven. Dis. **23:** 759, (Nov.) 1939.

12. Beerman, Herman: Fatalities Due to Bismuth in the Treatment of Syphilis, Arch. Dermat. & Syph. **26:** 797 (Nov.) 1932.

13. Vigne, Paul: Statistique des cas d'intolérance à la médication bismuthique observés au cours des ces cinq dernières années au dispensaire antivénérien de l'Hotel-Dieu de Marseille, Bull. Soc. franç. de dermat. et syph. (Réunion dermat de Strasbourg) **37:**1034 (July) 1930.

14. McCarthy, F. P., and Dexter, S. O., Jr.: Oral Manifestations of Bismuth, New England J. Med. **213:** 345 (Aug. 22) 1935.

15. Kimberly, L. W.: Accidental Intra-Arterial Injection of Bismuth in Oil with Demonstration of Bismuth by X-Rays in Arterioles of Penis, Am. J. Syph., Gonor. & Ven. Dis. **22:** 364 (May) 1938.

16. Skolnik, E. A., and Aleshire, Irma: Skin Eruptions from Bismuth Therapy in Syphilis, J. A. M. A. **98:** 1798 (May 21) 1932.

17. Nomland, Ruben; Skolnik, E. A., and McLellan, L. L.: Jaundice from Bismuth Compounds Used in the Therapy of Syphilis, J. A. M. A. **111:** 19 (July 2) 1938.

18. Wright, C. S.: The Effect of Bismuth Alone and in Combination with the Arsenobenzenes on the Wassermann Reaction, Am. J. M. Sc. **173:** 232 (Feb.) 1927.

19. Schamberg, J. F.: Bismuth and Neoarsphenamine in Syphilis and a Plea for More Conservative Dosage of the Arsenobenzenes, Arch. Dermat. & Syph. **20:** 431 (Oct.) 1929.

20. Sézary, A.: Le traitement mixte conjugé arséno-bismuthique dans la syphilis, Bull. Soc. franç. de dermat. et syph. (Réunion dermat. de Strasbourg) **37:** 981 (July) 1930.

21. Clausen; Tatum, A. L., and Longly, J. B.: Personal communication to the authors.

Table 1 compares the treatment schedule used at the University of Chicago Clinics with that proposed by the Cooperative Clinical Group [22] for adequate continuous treatment for early syphilis. The principal points in which the two plans differ are: (1) the simultaneous administration of bismuth and arsenical and the continuous administration of bismuth for the first forty to fifty weeks of treatment, (2) the short interval between all arsenical courses (never more than five weeks) and (3) the tapering off with four bismuth courses with increasing rest periods.

Table 1.—*Treatment Schedules for Early Syphilis*

Cooperative Clinical Group Continuous Treatment			University of Chicago Clinics Continuous Concurrent Treatment		
Weekly	Arsenical	Bismuth	Weekly	Arsenical	Bismuth
7	Ars. × 8		9	Ars. × 10	Bis. × 10
4		Bis. × 4	5		Bis. 2 cc. × 5
6	Ars. × 6		6	Ars. × 6	Bis. 1 cc × 6
6		Bis. × 6	5		Bis. 2 cc. × 5
6	Ars. × 6		6	Ars. × 6	Bis. 1 cc. × 6
8		Bis. × 8	5		Bis. 2 cc. × 5
6	Ars. × 6		6	Ars. × 6	Bis. 1 cc. × 6
10		Bis. × 10	4	4 weeks' rest	
6	Ars. × 6		10		Bis. 2 cc. × 10
10		Bis. × 10	12	12 weeks' rest	
			10		Bis. 2 cc. × 10
69	32	38	26	26 weeks' rest	
			10		Bis. 2 cc. × 10
			52	1 year's rest	
			10		Bis. 2 cc. × 10
			176	28	83

The 55 patients of whose treatment the results are summarized and compared with the Cooperative Clinical Group material (table 2) include all those who were under observation for over two years with an average observation time for the group of five years. There were 5 patients with seronegative primary, 9 with seropositive primary, 31 with early secondary, 6 with late secondary and 5 with early latent syphilis. Seven had had some previous treatment but of these all had positive blood reactions and 5 had active lesions when first seen.

Bismuth salicylate in oil was used intragluteally in all cases. In a few patients with secondary eruptions two to three preparatory injections of soluble bismuth were given before starting the regular schedule. Gruhzit,[23] Irgang [24] and more recently Kolmer [6] found that bismuth salicylate in oil is probably the best tolerated of the bismuth preparations, yet because of its slow absorption, repeated doses keep the tissue concentration as judged by urinary excretion (2 to 4 mg. per day [25]) at a therapeutic level over long periods of time.

The arsenical used must also be considered in evaluating the effect of bismuth in any course of combined treatment and is of particular interest in this series. In 80 per cent of the patients an experimental arsenical, thioarsine, was used entirely or in part. When used alone it was found to be unsatisfactory both from the standpoint of reactions and the clinical and serologic results as compared to arsphenamine.[26] Thus the role of bismuth seems to be relatively more important in our results. Four patients of the series were, for experimental reasons, treated with initial courses of thioarsine before any bismuth was given.

The statistical results given in table 2 for the Cooperative Clinical Group were taken or calculated from the most recent evaluation of their material by Stokes and Usilton [27] and include only the results from patients receiving continuous treatment who were under observation for over two years. The most significant figures for comparison are those showing the relative amounts of bismuth given, the percentage of final reversals of the blood Wassermann reaction and the percentage of probable cures.

Some further explanation of the results is necessary. The data may not be comparable since many of the 1,423 Cooperative Clinical Group patients, although receiving continuous treatment, may not have received the full recommended course, whereas almost all of our patients received treatment according to plan. The 143 patients mentioned as receiving ideal continuous treatment and observed for from two to ten years would be more nearly comparable, but unfortunately complete statistics were not given for this group. A retardation in the reversal of the blood Wassermann reaction when bismuth and arsenical compounds are used simultaneously, a point recently emphasized by Beerman,[28] was noted in our series. The 91 per cent final reversal of the blood Wassermann reactions given for the Cooperative Clinical Group study was computed inversely from the 123 patients who still had positive blood Wassermann reactions at the end of the period of observation.

Table 2.—*Comparison of Results in Treatment of Early Syphilis*

	Source of Data	
	University of Chicago Clinic	Cooperative Clinical Group Studies
Number of cases	55	—
Average number of arsenical injections	29	32 *
Average number of bismuth injections	79	38 *
Metallic bismuth equivalent	10.0 Gm.	3.0 Gm.
Percentage reversal of blood Wassermann reaction in 3 months	38%	52%† 1,423 patients
Percentage final reversal of blood Wassermann reaction	100%	91%†
Percentage of negative spinal fluid	100%	100%†
Number of cases	45 of 55	132 of 143
Complication of bismuth therapy	3 (5.4%)	—
Relapses	6 (9%)‡ 4 (7.4%)	7.7%† 143 patients
Irregular treatment §	8 (14%)	—
Time of observation	Over 2 years	Over 2 years†
Probable cures	100%	91% ? † 79.70%‖

* Continuous treatment recommended by the Cooperative Clinical Group.
† Stokes and Usilton.[27]
‡ Two patients had cutaneous relapses after lapses early in treatment before any bismuth had been given and should not be considered in evaluating bismuth therapy.
§ Missed 3 or more successive weeks in first year.
‖ Cooperative Clinical Group statistics cited by Moore.[5]

Of the 6 of our patients who relapsed, 2 were from the group of 4 previously mentioned who received an initial course of thioarsine without bismuth. Both had mucocutaneous relapses which occurred during this period. When combined treatment was given the lesions healed and the blood Wassermann and Kahn reactions

22. Stokes, J. H., and others: Cooperative Clinical Studies in Treatment of Syphilis: Early Syphilis, Ven. Dis. Inform. **13**: 165 (May 20); 207 (June 20); 253 (July 20) 1932.
23. Gruhzit, O. M., and Sultzaberger, J. A.: Bismuth Absorption, Distribution and Elimination, Am. J. Syph. **11**:103 (Jan.) 1927.
24. Irgang, S.; Alexander, E. R., and Sala, A. M.: Bismuth Compounds in the Treatment of Active Syphilis: A Clinical and Laboratory Study of Two Hundred and Eighty-Six Cases of Cutaneous Syphilis, Arch. Dermat. & Syph. **28**: 320 (Sept.) 1933.
25. Cole, H. N.; Sollmann, T., and Henderson, K.: Choice of a Bismuth Preparation, Am. J. Syph., Gonor. & Ven. Dis. **23**: 143 (March) 1939.
26. Becker, S. W., and Obermayer, M. E.: Clinical Observations on the Treatment of Syphilis by a Combination of Bismuth Salicylate and a New Arsenical Synthetic, Am. J. Syph. & Neurol. **19**: 505 (Oct.) 1935.
27. Stokes, J. H., and Usilton, Lida J.: Continuous and Intermittent Treatment in Early Syphilis, Ven. Dis. Inform. **18**: 66 (March) 1937.
28. Beerman, Herman: Lag in Reversal of Serologic Tests Under Bismuth in Course of Combined Chemotherapy, Am. J. Syph., Gonor. & Ven. Dis. **23**: 724 (Nov.) 1939.

rapidly became permanently negative. These patients should not be considered in evaluating the effect of bismuth, thus leaving only four (7.4 per cent) relapses. These 4 include 1 instance of iritis which appeared during the first combined course and healed in eight weeks without necessitating any modification of the treatment.

TABLE 3.—*Routine and Alternate Treatment Schedules for Syphilis of the Central Nervous System*

Routine Schedule			Alternate Schedule; Same as for Latent Syphilis		
Week	Arsenical	Bismuth	Week	Arsenical	Bismuth
5	Daily intravenous injection of sodium iodide, 25-100 cc. (10% solution) and daily intramuscular injection of soluble bismuth (bismuth sodium tartrate, 1 cc. of 1.5% solution)		10		Bis. × 10
4	Rest 4 weeks		4	4 weeks' rest	
6	Ars. × 6	Bis. × 6	6	Ars. × 6	Bis. × 6
4	Rest 4 weeks		4	4 weeks' rest	
8		Bis. × 8	8		Bis. × 8
4	Rest 4 weeks		4	4 weeks' rest	
6	Ars. × 6	Bis. × 6	6	Ars. × 6	Bis. × 6
4	4 weeks' rest		4	4 weeks' rest	
8		Bis. × 8	8		Bis. × 8
4	4 weeks' rest		4	4 weeks' rest	
6	Ars. × 6	Bis. × 6	6	Ars. × 6	Bis. × 6
	18	34		18	44

If cerebrospinal fluid is still positive, continue with courses of ten weekly injections of bismuth with two month rest periods indefinitely, plus tryparsamide or fever therapy if spinal fluid shows persistent preparetic changes.

If spinal fluid has become negative, taper off treatment with three courses of bismuth following increasing rest periods.

There were three serologic relapses. Two of these occurred after the six months rest period. They became and have stayed negative, one with further bismuth and autohemic injections, the other, with two courses of combined therapy, one course of bismarsen and three courses of a bismuth compound. The third patient relapsed during the three months rest period. The entire routine treatment was repeated, producing an early reversal. However, during his six months rest period, after the second course of treatment, the blood again showed a 1 plus Wassermann reaction on one occasion. This became negative with further bismuth courses only and has remained negative for five years.

All of our patients with the possible exception of 10 in whom the spinal fluid was not examined (all patients who relapsed had negative spinal fluids) fulfil the requirements for a "satisfactory result" as defined by Moore—"All patients with reinfection; all those satisfactorily completing a year of probation (no lesions of syphilis, repeated negative blood Wassermann reactions, negative cerebrospinal fluid, normal physical examination); a few patients who had entered on but not yet completed the probationary year, with all findings negative." [29]

Only 79.7 per cent "satisfactory results" were given by Moore [29] using these criteria in evaluating the Cooperative Clinical Group study. Stokes and Usilton [27] did not specifically mention any comparable figures, so the 91 per cent final reversal of the blood Wassermann reaction was also considered under percentage of probable cures.

The three complications due to bismuth that occurred were two instances of stomatitis and one gluteal abscess. No patients showed any significant urinary changes. A total of about 5,000 injections of bismuth compounds were given to the 55 patients. Two patients became jaundiced during treatment. In both a diagnosis of acute catarrhal jaundice was made, and arsenicals and bismuth compounds were later given without further difficulty.

29. Moore,[5] p. 188.

RESULTS OF TREATMENT OF ASYMPTOMATIC NEUROSYPHILIS AND TABES DORSALIS

Probably because of the advent of more spectacular and rapidly effective methods of treatment for syphilis of the central nervous system such as fever, intraspinal or tryparsamide therapy little work has been done on the effect of bismuth in these conditions. There are a few early references to the beneficial effect of bismuth alone or in combination with fever therapy in both active tabes dorsalis and dementia paralytica.[30] Recently [31] bismuth has been found the most effective drug for reversing the blood Wassermann reaction in syphilis of the central nervous system. As mentioned before, some physicians maintain that combined therapy gives fewer neurorecurrences and instances of late syphilis of the central nervous system. Bismuth has been demonstrated in the cerebrospinal fluid, and its passage into the nervous system seems to be facilitated by fever [32] and also by alcohol.[33]

The routine treatment for syphilis of the central nervous system as used in this study is outlined in table 3. When possible it was begun with five weeks' daily intravenous administration of iodides (25 to 100 cc. of a 10 per cent solution of sodium iodide and daily administration of soluble bismuth given intramuscularly (1 cc. of 1.5 per cent solution of bismuth sodium tartrate). If this was not feasible, the patient was given weekly injections of insoluble bismuth and iodides by mouth. Patients with clinical dementia paralytica or dementia paralytica fluid changes were, of course, immediately given fever therapy when possible. The fever treatment was then followed by routine chemotherapy as outlined.

TABLE 4.—*Asymptomatic Neurosyphilis (Late)*

	University of Chicago Clinics	Cooperative Clinical Group
Total number of cases	76	..
Sex	♂ 39 ♀ 37	♂ 298 ♀ 158
Reversal of cerebrospinal fluid reaction with routine treatment only *	71% 45 of 63	74% 152 of 203
Reversal with routine treatment plus tryparsamide therapy	50% 2 of 4	68% 32 of 47
Reversal with routine treatment plus fever therapy	75% 3 of 4	26% 22 of 82
Reversal with routine treatment plus fever plus tryparsamide therapy	33% 1 of 3	26% 9 of 34
Total reversals of spinal fluid reaction	72% 54 of 76	64.4% 364 of 565
Percentage receiving supplementary treatment	14% 11 of 76	64% of 565
Clinical or serologic progression	1.2% 1 patient	4.6% of 239 †
Average number of bismuth injections Bismuth equivalent (metallic)	100 12.0 Gm.	*

* For routine treatment see table 3. Cooperative Clinical Group minimum adequate treatment consists of 20 arsenicals and 20 heavy metal (bismuth) injections.

† Patients with late asymptomatic neurosyphilis who received adequate treatment.

30. Foster, L. J., and Smith, W. A.: Use of Bismuth in Treatment of Tabes and Paresis, J. Nerv. & Ment. Dis. **60**: 472, 1924.

31. Belding, David L.: Effect of Antisyphilitic Drugs on the Wassermann Test, Am. J. Syph., Gonor. & Ven. Dis. **24**: 29 (Jan.) 1940.

32. Klauder, J. V., and Brown, Herman: The Question of Bismuth Penetration of the Nervous System, Arch. Dermat. & Syph. **29**: 351 (March) 1934.

33. Newman, H. W., and Richardson, A. P.: Effect of Alcohol on Penetration of Bismuth into the Central Nervous System, Am. J. Syph. **21**: 77, 1937.

The "basic" routine therapy just mentioned does not differ greatly in amount from that considered by the Cooperative Clinical Groups as "minimal prescribed routine treatment," [34] which consists of twenty arsenical and twenty to forty heavy metal injections. Further therapy, however, consists again of the prolonged administration of bismuth compounds, specifically: If the cerebrospinal fluid is still positive after the basic routine treatment, courses of ten weekly intramuscular injections of bismuth compounds with two month rest periods are continued until it becomes negative unless there is evidence of clinical progression or the spinal fluid shows persistent predementia paralytica changes, in which case fever therapy is given. Routine treatment as referred to in tables 4 and 5 should be interpreted as meaning the "basic" bismuth-arsenical courses plus all further bismuth, i. e. all treatment except fever, intraspinal or tryparsamide therapy.

TABLE 5.—*Comparison of Results in Tabes Dorsalis*

	University of Chicago Clinics — Type of Treatment			Cooperative Clinical Group * — Type of Treatment		
	Routine †	Routine Plus Intensive ‡	Total	Routine §	Routine Plus Intensive ‡	Total
Number of patients.....	79% 53	21% 14	100% 67	28% 266	72% 702	100% 968
Clinically arrested or improved	60% 32	36% 5	56% 38	—	—	55%
Clinically stationary....	35% 19	28% 4	34% 23	—	—	—
Clinically progressive....	4% 2	36% 5	10% 7	18%	13%	14%
Spinal fluids never positive	6	..	6	—	—	—
Spinal fluids not reexamined	12	2	14	—	—	—
Spinal fluid reversals....	62% 22 of 35	50% 6 of 12	60% 28 of 47	60%	..	54%
Average number of bismuth injections	..	..	120			
Average time of observation	..	..	Over 3 yrs. 6	..	..	Over 2 yrs.

* Statistics taken or estimated from Cooperative Clinical Group study, O'Leary.[34]

† See table 3.

‡ Intensive therapy included at University of Chicago Clinics tryparsamide and fever—malaria or typhoid—therapy; in Cooperative Clinical Group material it included tryparsamide, malaria and intraspinal therapy.

§ Twenty arsenical and forty heavy metal injections.

Tables 4 and 5 compare our results in the treatment of asymptomatic neurosyphilis and tabes dorsalis with as nearly comparable data as possible taken from the Cooperative Clinical Group studies: [35] A detailed analysis of cases based on the type of spinal fluid changes found was not significant in any of our data because of the comparatively small series. However, both the percentage distribution of the type of change found and the conclusion that the more severe the spinal fluid changes the more resistant they were to treatment were the same in both series. The important points brought out by both table 4 and table 5 are that not only do our final results appear better, as gaged by reversal of the changes in the spinal fluid and the low percentage of clinical and serologic progression, but these results are attained in a high percentage of cases by the prolonged use of bismuth alone rather than by the use of the more dangerous intensive measures such as fever, intraspinal and tryparsamide therapy.

34. O'Leary, P. A., and others: Cooperative Clinical Studies in the Treatment of Syphilis: Asymptomatic Neurosyphilis, Ven. Dis. Inform. **18**: 45 (March) 1937.

35. O'Leary, P. A., and others: Cooperative Clinical Studies in the Treatment of Syphilis: Tabes Dorsalis, Ven. Dis. Inform. **19**: 367 (July) 1938; footnote 34.

Many of our patients received truly massive doses of bismuth compared to the amount usually given, and the question of renal damage as the most likely serious result of chronic bismuth intoxication must be considered. The averages in metallic bismuth equivalents given for early syphilis, asymptomatic neurosyphilis and tabes dorsalis were 10 Gm. in three years, 13 Gm. in six years and 15.2 Gm. in six years respectively. The largest amount received by any 1 patient was approximately 35 Gm. over a period of eleven years. Periodic routine examinations of the urine were performed on all patients receiving antisyphilitic therapy. Although some patients occasionally showed traces of albumin there has been no evidence of serious renal damage. Several years ago at the suggestion of Dr. Cole renal function tests were made on several patients under treatment who had received considerable bismuth and the patients' kidneys were found to be normal. At the present time there is no evidence that there are any toxic effects from these large doses of bismuth.

SUMMARY

The twenty years experience with bismuth in syphilis therapy has shown that, although in some instances it will "cure" syphilis, it cannot be relied on as the sole antisyphilitic drug to the exclusion of the arsphenamines. Extensive studies of the many bismuth compounds advocated for intramuscular use indicate that the effectiveness of any one preparation depends on the ionizable bismuth which it makes available in the body. At the present time the consensus of opinion seems to be that bismuth salicylate in oil is the most suitable from the standpoint of the therapeutic effect, low toxicity and prolonged action.

Of the many complications reported from bismuth therapy, oral lesions and local manifestations at the site of injection are by far the most common though seldom serious. The greater proportion of complications could be avoided by proper oral hygiene and careful injection technic.

The method for the treatment of early syphilis presented differs from the usual one chiefly in the use of combined bismuth-arsenical courses, the continuous use of bismuth for the first forty to fifty weeks and tapering off of treatment with bismuth. About twice the usual amount of bismuth is used. The results of treatment of 55 patients with early syphilis by this method compare favorably with those of the Cooperative Clinical Group study for the continuous treatment of early syphilis. The respective percentages for the two systems were: final reversal of blood Wassermann reaction, 100 per cent and 91 per cent; relapses, 7.4 per cent and 7.7 per cent, and satisfactory result, 100 per cent and 79.7 per cent.

The results of a system of treatment for asymptomatic neurosyphilis and tabes dorsalis which uses prolonged bismuth therapy in place of the intensive measures such as fever, intraspinal and tryparsamide therapy also compared with the Cooperative Clinical Group results, in both instances the percentages of spinal fluid reversals, of progressions and clinical improvement being slightly in favor of the bismuth therapy. However, the important point is that bismuth produced these results in a great majority of patients without the use of fever, intraspinal or tryparsamide therapy.

The large amounts of bismuth received by these patients in no case caused any serious reaction or intoxication.

1900 Indianapolis Boulevard—950 East Fifty-Ninth Street.

ABSTRACT OF DISCUSSION

DR. DONALD M. PILLSBURY, Philadelphia: Sobisminol mass has been approved by the Council on Pharmacy and Chemistry in the treatment of syphilis. It has been shown to exert a potent spirocheticidal effect in experimental syphilis. The experimental results have been good with the exception of those of Kemp, who did not find an adequate spirocheticidal effect in rabbit syphilis. I have used sobisminol mass by mouth in 87 cases of congenital syphilis. I have no clinical indication that it is not a potent antisyphilitic agent. In common with the general criticism of treatment by mouth, I think one cannot be certain that the treatment is administered as directed. It had been hoped that with a rapid method of bismuth determination in the urine which has been reported on by Hanzlik and his co-workers it would be possible to determine whether or not patients were actually receiving the bismuth, as directed. I have found that the determination of the bismuth on individual samples of urine is absolutely without value in this regard. Patients in the ward who I was certain were being given the drug gave occasional negative results in the urine or a very low bismuth concentration was noted. This finding is also noted in the report of Barnett. I am at present continuing the use of sobisminol mass by mouth only for patients kept in the wards of the hospital who I can be certain are being given the bismuth compound and on whose urine determination on twenty-four hour samples can be made. Very large doses of sobisminol mass are necessary for children; older children are given the dose which is ordinarily employed for adults, that is 1,200 mg. of the mass daily. One objection to this type of therapy has been the high incidence of gastrointestinal reactions, not severe, not always necessitating discontinuance of this type of treatment, but certainly discouraging. This has occurred in over 25 per cent of the cases. Another objection to this method of therapy is that the cost of the drug is high, about 5 cents a capsule, and with 3 to 6 capsules a day being given, this amounts to a drug cost of 1 to 2 dollars weekly.

DR. S. WILLIAM BECKER, Chicago: The series which we have presented is very small, but we feel that our results have been good and the treatment is devised so that it can be administered in an office without a great deal of equipment and without hospital facilities. As a matter of fact, this treatment was devised because we do not have facilities for intraspinal therapy. We have a small hospital service, so that we could not hospitalize patients for hyperpyrexial therapy. We do not feel that tryparsamide should be used except when other methods are contraindicated. I have felt for a long time that a combination of arsenical and bismuth therapy in syphilis is efficacious and tends to prevent relapses. Tatum has recently, as Dr. Walsh has stated, verified our impressions in the laboratory. The combination of arsenical and bismuth therapy from the therapeutic standpoint is additive but from the toxic standpoint it is not additive, evidently because the two drugs affect different organs in the body. Our present inclination is to start the treatment of early syphilis immediately with mapharsen and a soluble bismuth compound. The patient seen with the primary lesion or with very early secondary syphilis is given mapharsen and a soluble bismuth compound every other day for three injections and then treatment is continued at five day intervals. It is surprising that we have been able to give large amounts of bismuth, insoluble bismuth, without encountering any serious difficulty. This was impossible in the case of mercury. The patient who was given insoluble mercury intragluteally for some reason or other would suddenly have a large amount of this material absorbed, and toxic symptoms would be produced. We have never observed this particular complication in connection with bismuth therapy.

Some of the Contents of Cheese.—Whilst butter contains little more than the fat of the milk, cheese contains the casein, a large proportion of the valuable mineral salts and an important part of the vitamins as well.—*Nature*, Dec. 21, 1940, p. 796.

THE NATURE AND PATHOLOGY OF RADIATION SICKNESS

VIRGIL H. MOON, M.D.
KARL KORNBLUM, M.D.
AND
DAVID R. MORGAN, M.D.
PHILADELPHIA

It has been known for years that severe, sometimes fatal illness may develop in patients subjected to intensive irradiation. Weakness, nausea, vomiting, oliguria, bloody diarrhea, rapid feeble pulse, low blood pressure and profound prostration are prominent clinical features. Both the metabolism and the renal elimination of wastes are markedly reduced. It has been observed that exposure of the abdomen to roentgen rays caused signs of illness more often than exposure of other areas. Death results from circulatory failure resembling that produced by anaphylaxis, severe intoxications, burns or intestinal obstruction.

Space is lacking to discuss the various theories offered as explanations and the extensive experimentation done in search for further evidence. Those interested in these matters are referred to reviews.[1] Hall and Whipple [2] and Warren and Whipple [3] noted that the manifestations after extensive irradiation were like those of heat burns but with this difference: The latter produce illness immediately, while radiation sickness develops after a latent period. They noted also that the signs of illness resulting from acute intestinal obstruction are exactly like those following deep abdominal radiation. They showed that the latter produced delayed necrosis of the glands and of the epithelium in the intestinal mucosa and ascribed the illness to the absorption of products of cellular disintegration. The mechanism of this effect was like that which Whipple had shown in experiments on closed intestinal loops.

We were impressed by the close resemblance between the manifestations of radiation sickness, high intestinal obstruction or strangulation and those of shock resulting from various causes. We have reported [4] on the development of shock incidental to intestinal obstruction. It seemed of interest to compare both the physiologic disturbances and the postmortem findings of radiation sickness with those which characterize shock. Our initial experiments were arranged to duplicate closely the roentgen technic employed by Whipple. The physical factors employed were 130 kilovolts, 5 milliamperes, 2 mm. of aluminum filter, and 30 cm. skin-target distance. The output of the equipment was 72 roentgens per minute. Open field irradiation was given over the abdomen of healthy, normal dogs in amounts ranging from 1,400 to 2,800 roentgens. These amounts were given in one application divided between two abdominal areas.

No effects were observed for twenty-four to sixty hours, after which signs of illness developed. There were loss of appetite, vomiting, diarrhea and a decrease in the output of urine. Traces of blood were seen in

From the Departments of Pathology and Roentgenology, Jefferson Medical College and Hospital.

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1. Rolleston, H.: Harmful Effects of Irradiation: Critical Review, Quart. J. Med. **24:** 101, 1930. Desjardins, A. U.: Action of Roentgen Rays and Radium on the Gastro-Intestinal Tract, Am. J. Roentgenol. **26:** 145, 335 and 493, 1931.

2. Hall, C. C., and Whipple, G. H.: Roentgen Ray Intoxication, Am. J. M. Sc. **157:** 453, 1919.

3. Warren, S. L., and Whipple, G. H.: Roentgen Ray Intoxication, J. Exper. Med. **38:** 713, 1923.

4. Moon, V. H., and Morgan, D. R.: Shock: The Mechanism of Death Following Intestinal Obstruction, Arch. Surg. **32:**776 (May) 1936.

the urine, feces and vomitus. This blood was derived from capillary hemorrhages in the mucosae and was not of sufficient amount to affect significantly the total blood volume. Concentration of the blood was manifested by a progressive increase in the hemoglobin content and in erythrocyte counts. These symptoms progressed

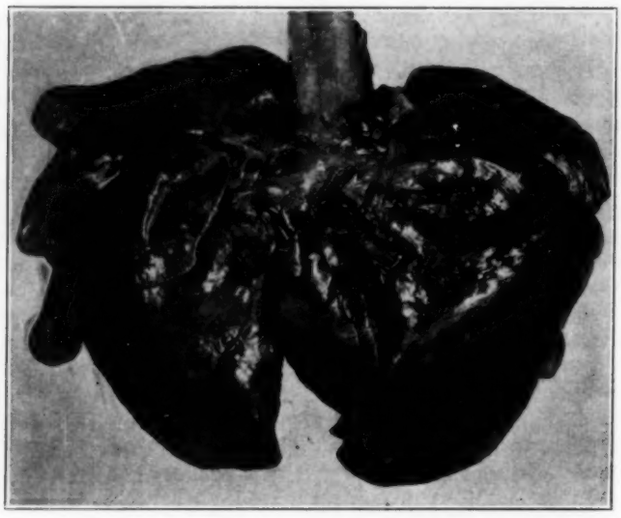

Fig. 1.—Lungs of a dog after death by radiation sickness. All parts of the lung and the serous surfaces show diffuse capillovenous congestion.

and death from circulatory failure occurred usually within twenty-four hours after the onset of illness.

It has been shown [5] that hemoconcentration is the earliest and most significant clinical sign of shock arising from any cause whatsoever. Accordingly, counts of red cells and hemoglobin estimates were made before irradiation for comparison with subsequent data. There was no disturbance in the state of the blood until the onset of symptoms. At this point hemoconcentration appeared regularly and progressed commensurately with the severity of the symptoms. The hemoconcentration ranged from 15 to 50 per cent. The signs of illness and other data in a typical experiment,

Fig. 2.—Section of lung in figure 1, showing marked capillovenous congestion and edema.

dog 293, the first animal treated, are shown in table 1. The results of abdominal irradiation were concordant in all animals. These are summarized in table 2.

Postmortem examination showed a diffuse congestion of the viscera. The lungs were mottled and cyanotic in appearance (fig. 1). Microscopic examination showed capillovenous congestion and numerous capillary hemorrhages. The serous surfaces and the gastrointestinal mucosa were deeply congested. There was bloody fluid in the intestinal lumens, and the lining had the appearance of purple velvet. The evidences of damage were most pronounced in the mucosa of the small bowel. Microscopic examination showed varying degrees of degeneration and necrosis of the epithelium and congestion of the capillaries and venules. The liver and kidneys showed parenchymatous degeneration and congestion. The spleen was contracted and bloodless. No significant changes were seen in other organs. These are the characteristic appearances of the viscera in shock from all causes excepting hemorrhage.[6]

A dose of 1,860 roentgens given as described caused death regularly in three to five days. One dog (295) given 1,116 roentgens showed moderate illness and hemoconcentration followed by recovery. A dog (296)

TABLE 1.—*Data Concerning Dog 293*

Date		Signs of Illness	Temperature	Hemoglobin, Mg. per 100 Cc.	Leukocytes	Erythrocytes
5/1		Normal, before treatment	101.2	12	11,400	5,860,000
5/2	5:00 p. m.	Normal, before treatment	101.2	12	12,200	5,830,000
Irradiated	5:00 p. m.					
5/3	8:30 a. m.	No signs of illness	101.0	13	12,100	6,180,000
	4:00 p. m.	No signs of illness	101.5	13	11,100	6,440,000
5/4	9:00 a. m.	Vomited during night	101.0	13	12,350	6,200,000
	4:00 p. m.	Eats only part of food	101.4	13	9,800	6,180,000
5/5	9:00 a. m.	Vomited during night	101.0	13	10,000	6,060,000
	4:30 p. m.	Refuses food	101.6	13	10,900	6,070,000
5/6	8:30 a. m.	Urine scanty, blood tinged; vomitus contains blood	101.6	18	6,250	7,230,000
	12.00 m.	Diarrhea blood tinged; pulse rapid, extremities cold, dog very ill	102.0	18+	4,000	7,950,000

The animal was given 2,772 roentgens over the abdomen May 2, 1939 and died at 12:30 p. m., May 6.

given 1,488 roentgens showed more serious illness and hemoconcentration. It lost 20 per cent of body weight and died of terminal pneumonia thirteen days later. Thus 1,860 roentgens, applied to the abdomen, appeared to be the approximate lethal dose for dogs.

In one group of 7 dogs, radiation was given over the liver, the lower part of the abdomen being protected by lead shields. In 1 of these animals (331) fatal illness accompanied by hemoconcentration developed. The postmortem observations were the same as those described previously. In another (333) slight illness developed accompanied by 12 per cent hemoconcentration, but the dog recovered. The remaining dogs in this group showed no hemoconcentration or evidence of illness. In 2 dogs (336 and 337), the liver and adrenals were shielded and the irradiation confined to the lower abdomen. These animals manifested typical reactions accompanied by hemoconcentration and followed by death. No illness resulted in 2 dogs (297 and 298) given 1,860 roentgens and 3,720 roentgens respectively

5. Moon, V. H.: Occurrence and Clinical Significance of Hemoconcentration, Ann. Int. Med. **13**: 451, 1939.

6. Moon, V. H.: Shock and Related Capillary Phenomena, New York, Oxford University Press, 1938.

over the chest. These experiments corroborate the observations of Whipple and of others that the intestinal mucosa is more sensitive than other tissues to the injurious effects of irradiation.

One group of dogs (302, 303, 304 and 305) were treated as described but were killed at intervals of twenty-four to eighty-eight hours after exposure. This was done in order to make examinations of the intestinal mucosas at earlier stages after the injury. Sections of bowel and of other tissue were placed in fixative within five minutes of the death of the dogs.

leukopenia develops in cases of severity, while in the early stages and in sublethal degrees of shock, leukocytosis is often seen. In most of the experiments with fatal outcome, the number of leukocytes declined before death. In several nonfatal experiments there was a sharp rise in the leukocyte counts.

COMMENT

Some of the theories offered in explanation for radiation sickness have been purely conjectural and unsupported either by logic or by evidence. Thus

TABLE 2.—*Summary of the Results of Experiments on Radiation Sickness*

Dog	Dose, Roentgens	Area	Illness Began	Hemoconcentration	Leukocytes	Results
293	2,772	Abdomen	In about 48 hours	Began 48 hours Maximum: 50%	11.4 M, decline to 4.0 M	Death, 91 hours
294	1,860	Abdomen	After 60 hours	Began 24 hours Maximum: 25%	14.0 M, decline to 4.0 M	Death, 87 hours
295	1,116	Abdomen	After 60 hours	Began 42 hours Maximum: 16%	10.9 M, decline to 9.0 M	Moderate illness, recovery
296	1,488	Abdomen	After 84 hours	Began 90 hours Maximum: 20%	19.0 M, decline to 4.3 M, rose to 13.6 M	Severe sublethal shock; death, 322 hours
299	1,860	Abdomen	After 88 hours	Began 88 hours Maximum: 21%	5.7 M, decline to 2.5 M	Death, 96 hours
301	1,860	Abdomen	After 84 hours	Began 64 hours Maximum: 20%	9.5 M, decline to 6.1 M	Death, 111 hours
306	1,852	Abdomen	After 64 hours	Began 48 hours Maximum: 33%	8.1 M, rose to 15.2 M, decline to 5.3 M	Death, 115 hours
324	2,160	Abdomen	After 48 hours	Began 48 hours Maximum: 21%	10.0 M, decline to 5.0 M	Death, 67 hours
329	2,160	Abdomen	After 80 hours	Began 88 hours Maximum: 30%	No data	Death, after 4 days
302	1,860	Abdomen	None	None	7.0 M, rose to 8.0 M	Killed for examination after 66 hours
303	1,860	Abdomen	None	None	17.0 M, decline to 10.0 M	Killed after 40 hours
304	1,860	Abdomen	After 48 hours	Began 48 hours Maximum: 16%	10.0 M, rose to 18.8 M	Killed after 88 hours, when very ill
305	1,860	Abdomen	None	None	No significant change	Killed for examination after 24 hours
297	1,860	Chest	None	None	13.7 M, decline to 6.8 M, rose to 10.4 M	Recovery
298	1,860	Chest	None	None	10.0 M, decline to 5.4 M	Recovery
315	926	Liver only	None	None	No change	No signs of illness
318	1,852	Liver only	None	None	No change	No signs of illness
320	2,778	Liver only	None	None	No change	No signs of illness
322	2,778	Liver only	None	None	No change	No signs of illness
331	1,852	Liver only	On 4th day	Began 96 hours Maximum: 23%	No data	Death after 4 days
333	1,852	Liver only	Moderate, 72 hours	Began 72 hours Maximum: 12%	No change	Recovery
336	1,852	Liver only	None	None	8.5 M, rose to 10.6 M	No signs of illness
335	1,852	Abdomen only; adrenals shielded	After 48 hours	Began 36 hours Maximum: 20%	No data	Death about 60 hours
337	1,852	Abdomen only; adrenals shielded	After 40 hours	Began 36 hours Maximum: 30%	10.9 M, decline to 9.0 M	Death about 60 hours

Study of such sections confirmed the findings of Whipple and his associates, who made similar studies. The evidences of damage were most obvious in the mucosa of the small bowel (fig. 3). The epithelium lining the crypts and covering the villi showed all stages of disintegration and destruction. Some crypts contained nuclear and cellular débris; others were empty. Some of the villi retained their epithelial covering while that in the crypts showed necrosis and disintegration. Other villi were completely denuded of their epithelial covering (fig. 4).

In most instances there were no significant changes in the rectal temperature. The leukocyte reactions varied in a fashion similar to those described in clinical and in experimental shock.[6] It has been shown that the suppositions that such illness results from the inhalation of ozone or other gases generated by the electric apparatus or that the patient is allergic to roentgen rays deserve little attention; likewise, the supposed effects of static electricity in the body, the presence of a "roentgen toxin" in the blood, the effect of glycogen depletion and endocrine imbalance.

Other attempts to explain the phenomena were based on similarities to known conditions. Thus the resemblance of radiation sickness to acute poisoning, to the effects of burns, of physical trauma, of profound intoxication, of anaphylaxis or of intestinal obstruction were comparisons based on clinical observations. Radiation sickness has items of pathologic physiology in common with each of those conditions, and the clinical features

present no characteristic differences. An increase in the nonprotein nitrogen, hydrogen ion concentration, dextrose, phosphorus and potassium content of the blood and a decrease in the chloride content, oxygen content, metabolism and in the total blood volume are found in the conditions mentioned, also in radiation sickness and in shock from various causes.

Many years ago, Edsall and Pemberton [7] interpreted radiation sickness as a toxic reaction to products of cellular disintegration. Later Hall, Warren and Whipple conducted extensive experiments on the subject and came to the conclusion noted earlier in this paper. Rolleston [1] reviewed the various proposed explanations and found that the weight of evidence favored acute toxemia from products of cellular injury or destruction. These products, as shown by Lewis, cause dilatation and increased permeability of capillaries. This effect, if extensive, results in decreased blood volume, increased concentration of the blood, reduced volume flow and reduced delivery of oxygen, producing tissue anoxia, and thereby the mechanism of shock is initiated.[6]

Forfota and Karády [8] cited numerous observations on the resemblance between radiation sickness and shock. They commented on the demonstrations by Ebbecke,[9] Lewis [10] and others that cellular injury of any kind causes the release of H substances which affect capillaries in the same fashion as does histamine. They compared the effects of histamine and of experimental radiation in dogs and reported that examinations of the blood showed the same essential variations from normal.

Our results have confirmed those of the authors cited; furthermore, our interpretations are similar. Exposure of the abdominal viscera to massive doses of roentgen irradiation causes delayed necrosis of the intestinal mucosa. Absorption of cytoplasmic material from this damaged tissue seems to produce the physiologic disturbances noted. The severity of the illness seems to parallel the recognizable epithelial injury. The resulting symptoms are those regularly seen in shock from other causes. The condition is accompanied by progressive hemoconcentration, and the visceral changes seen post mortem are characteristically those of circulatory failure of the shock type.

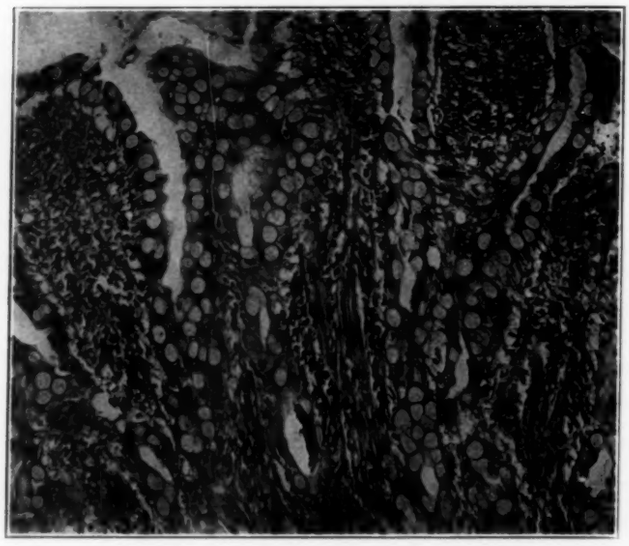

Fig. 3.—Mucosa of the small bowel of a dog (305) killed twenty-four hours after abdominal irradiation. Mucoid degeneration of the epithelial lining is present.

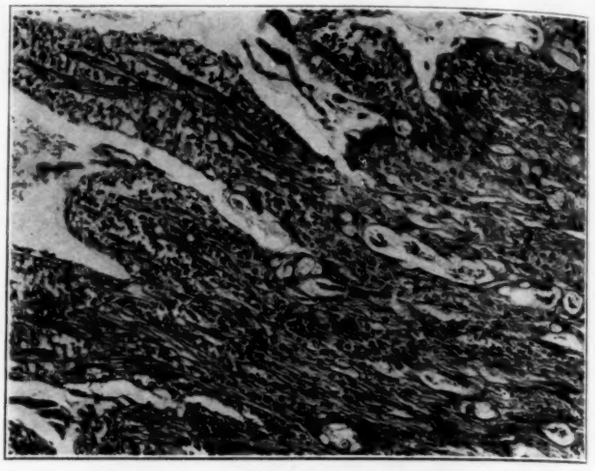

Fig. 4.—Intestinal mucosa of a dog (302) killed sixty-six hours after abdominal irradiation. The cells of the glands have disintegrated and the villi are denuded of their epithelial covering.

These experiments have a significant bearing on the mechanism of shock. Some writers assign this to local hemorrhage and loss of fluid or to sympathoadrenal hyperactivity and disregard absorption of products from damaged tissues as a factor. Injury to the intestinal mucosa by irradiation is like injury by heat or other physical agents, but with these differences: it produces delayed necrosis and causes no pain or emotional reactions. Hence such injury eliminates hemorrhage, anesthesia, pain, emotional reactions and sympathoadrenal hyperactivity as factors. In such experiments it appears that the disturbances of circulation result solely from absorption, independently of other factors.

SUMMARY

Exposure of the abdomen to high voltage roentgen irradiation causes physiologic disturbances like those of shock arising from other causes. This is accompanied by progressive hemoconcentration. The visceral findings post mortem are those characteristic of shock regardless of its origin. Deep roentgen irradiation causes delayed necrosis of the intestinal mucosa. The resulting signs of illness are likewise delayed in onset.

Irradiation provides a new method for inducing shock by injury to living tissues. This method eliminates the confusing effects of other factors including pain, emotional reactions, sympathoadrenal hyperactivity, hemorrhage and anesthesia.

ABSTRACT OF DISCUSSION

DR. CHARLES L. MARTIN, Dallas, Texas: Radiation sickness is of great interest to me because I have participated in a number of studies made on irradiated animals during the past twenty years. In 1919 Dr. Willey Denis and I investigated the blood chemistry of rabbits killed with large doses of roentgen rays given over the abdomen at the Massachusetts General Hospital. The blood concentration described by the authors was noted and was ascribed to a dehydration resulting from a severe diarrhea and an anorexia. The animals refused food and water and showed a suppression of urination and a loss of weight. It is my impression that this syndrome is not the same as that seen in shock. Small animals may be killed with doses of roentgen rays which produce no demonstrable change in the intestine, and death must be due to chemical or

7. Edsall, D. L., and Pemberton, R.: Nature of the General Toxic Reaction Following Exposure to X-Rays, Am. J. M. Sc. **133**: 426, 1907.

8. Forfota, E., and Karády, S.: Ueber die biologische Allgemeinwirkung der Röntgenstrahlen vom Gesichtspunkte einer durch Histamin oder ähnlich wirkende Substanzen verursachten Schockwirkung, Strahlentherapie **59**: 258, 1937.

9. Ebbecke, U.: Die lokale vasomotorische Reaktion der Haut und der inneren Organen, Arch. f. d. ges. Physiol. **169**: 1, 1917; Capillärerweiterung, Urticaria und Schock, Klin. Wchnschr. **2**: 1725, 1923.

10. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, Ltd., 1927.

physiologic changes. Experiments that Dr. Fred Rogers and I reported a good many years ago proved that damage to the adrenal glands did not produce the fatal outcome. Although the mechanism of the process is still not understood, some work done recently at Baylor University with Dr. Walter Moursund convinces me that a vitamin B deficiency is one of the factors involved, and large doses of thiamine hydrochloride are of real value in the treatment of many patients suffering from radiation sickness. The Cincinnati group has been interested in this phase of the problem and I am told that they will soon bring forth some new helpful information. Certainly this field of investigation is still a fertile one.

DR. DAVID I. MACHT, Baltimore: In 1939 I published a paper on the blood pharmacology after exposure to roentgen rays. By using special pharmacologic methods which I have developed and have been using for some twenty years, in which living plant test objects are used for testing toxicity of the blood, I have examined the normal blood serum of various animals—dogs, cats, rabbits, guinea pigs, rats, mice and other animals—before and after exposure to various doses of roentgen rays. The results are interesting. One can show quantitatively and by experimental means (phytopharmacology is what I call this method) that there is a toxin, or at least a toxic reaction, developed in the blood, not immediately but twenty-four hours after exposure to the rays. That declines after a few days, depending on the dose. I thought it necessary to make these experiments on normal animals before going to clinical observations, and during the past two years I have collected some data of a clinical nature. I have examined by the same method twenty clinical cases, blood specimens from the Johns Hopkins X-Ray Clinic, some of malignant disease and others of benign conditions treated with roentgen rays, and all of them showed this toxic reaction. Furthermore, I have examined the blood of apparently normal persons, namely, roentgen ray specialists, physicians, nurses and workers in the roentgen ray laboratories. I took serums and tested them by phytopharmacologic methods, and all of them showed a toxic reaction. That is remarkable, because they were not complaining of anything, but it shows that roentgen rays do produce intricate biologic changes. I wish to add that such work as is being done by Wallace and Moon and their co-workers, and perhaps these attempts of mine on pharmacologic lines, are the kind necessary for combating or at least considering methods for rational therapeutic treatment of roentgen ray sickness, because these are the best objective criteria by which one can measure the blood or pathologic changes and tell whether the method of treatment is really effective or imaginary.

DR. ROSS GOLDEN, New York: Dogs, like human beings, may be made ill with very moderate doses of roentgen rays. In the winter of 1920-1921, in trying to investigate the question of acidosis as a cause of roentgen sickness, I had occasion to irradiate the upper abdomen of dogs. I found that by giving about what I thought was a human erythema dose at that time, probably somewhere around 400 or 500 roentgens, the dog could be made to vomit consistently about a half hour after irradiation was given. That could be kept up for a number of weeks. These dogs became emaciated and finally died, but it was three or four months after the inauguration of the experiments. These immediate effects on the dogs resembled clinical roentgen sickness, and it is rather difficult for me to correlate them with the authors' findings. I have seen patients get sick with 75 roentgens over the chest. I am wondering whether the authors could say something about the relationship of these moderate doses to obvious roentgen ray sickness. Perhaps they have some ideas about the immediate reaction, not a delayed reaction, which must be responsible for it.

DR. MOSES F. LUBELL, Waterville, Maine: I should like to ask the authors and Dr. Wallace what therapeutic agents they now recommend and whether they have had any experience with nicotinic acid.

DR. ROBERT P. NOBLE, Raleigh, N. C.: Why is it that some people do not get sick from small doses?

DR. VIRGIL H. MOON, Philadelphia: Let it be emphasized that we were interested in the acute manifestations. We made no observations on the late or delayed results such as nutritional or metabolic deficiencies. We were interested in the syndrome as described that manifested itself by nausea, vomiting, diarrhea, low blood pressure, prostration and so on. We have not conducted any studies on the minor degrees either of that syndrome or of the late effects which lesser dosage of roentgen rays would produce at longer intervals of time. I was interested in Dr. Macht's observation concerning a toxemic factor. You will recall that the theory of traumatic toxemia of shock held the attention of medical men for a number of years after the World War. Later that idea was replaced to some extent by evidence which now has been discredited, and the original evidence has been confirmed. We now believe that shock resulting from trauma, from burns, from prolonged surgery or, as in this instance, from severe damage to the gastrointestinal tract by roentgen rays is due to some agent which exerts toxic effects on the endothelium of the circulatory system; and so, Dr. Macht, the idea of a toxic substance or toxic reaction is not out of our picture at all. I am deeply interested in the phytopharmacologic reaction that you mentioned, because certain other workers have used that test in histamine shock and in shock produced by other agents. They demonstrated by phytopharmacologic methods a toxic effect on young growing plants. In reply to Dr. Golden, our experiments were not designed to test the sublethal or late effects of irradiation. That is an important subject, but it does not have a direct bearing on this syndrome of circulatory collapse which develops incident to deep abdominal irradiation. Dr. Lubell, we have undertaken no therapeutic experiments either. We were concerned with the mechanism and have made no attempts at treatment. I am sure we will all agree with you, Dr. Noble; we should all like to know why some people do not get sick under the same circumstances which provoke illness in the average or normal person.

THE VIRUS OF POLIOMYELITIS IN STOOLS AND SEWAGE

JOHN R. PAUL, M.D.
AND
JAMES D. TRASK, M.D.
NEW HAVEN, CONN.

During the past two years it has become increasingly apparent that the virus of poliomyelitis may be readily isolated from stools of patients with poliomyelitis. Many reports [1] now testify to the ease with which this may be accomplished, not only from the stools of patients with the paralytic type [2] but also from those of patients with the common abortive type.[3] In fact the stool method has quickly found its place in the study of this disease, and during this short period of time our knowledge of human carriers has been considerably enhanced. Already Lépine [4] in Paris has followed one child con-

From the Departments of Internal Medicine and Pediatrics, Yale University School of Medicine.

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1. Harmon, P. H.: The Use of Chemicals as Nasal Sprays in the Prophylaxis of Poliomyelitis in Man, J. A. M. A. **109:** 1061 (Sept. 25) 1937. Kramer, S. D.; Hoskwith, B., and Grossman, L. H.: Detection of the Virus of Poliomyeltis in the Nose and Throat and Gastrointestinal Tract of Human Beings and Monkeys, J. Exper. Med. **69:** 49 (Jan.) 1939. Trask, Vignec and Paul.[2] Kling, Olin, Magnusson and Gard.[3] Lépine, Sédallian and Sautter.[4] Kramer, Gilliam and Molner.[5]

2. Trask, J. D.; Vignec, A. J., and Paul, J. R.: Poliomyelitis in Human Stools, J. A. M. A. **111:** 6 (July 2) 1938. Harmon.[1]

3. Kling, C.; Olin, G.; Magnusson, J. H., and Gard, Sven: Nouvelles recherches sur l'élimination du virus poliomyélitique par matières fécales, Bull. Acad. de méd., Paris **121:** 826 (June 13) 1939. Trask, Vignec and Paul.[2] Lépine, Sédallian and Sautter.[4] Kramer, Gilliam and Molner.[5]

4. Lépine, Pierre; Sédallian, P., and Sautter, V.: Sur la présence du virus poliomyélitique dans les matières fécales et sa longue durée d'élimination chez un porteur sain, Bull. Acad. de méd. Paris **122:** 141 (July 18) 1939. Poliomyelitis, Foreign Letters (Paris), J. A. M. A. **113:** 1046 (Sept. 9) 1939.

valescent from abortive poliomyelitis who harbored the virus in the intestinal tract as long as one hundred and twenty-five days, and Kramer and his co-workers,[5] more recently in Detroit, have given a convincing report of "healthy intestinal carriers" in this disease. These observations point the way toward at least two lines of investigation which should throw light on the manner in which poliomyelitis spreads. One of these lines of approach lies in the clinical use of examination of the stool as a diagnostic test for detecting certain patients with poliomyelitis who have been overlooked and carriers of the virus of poliomyelitis; the other concerns the fate of the virus after it leaves the patient and "leaves the stool," as it were. For, obviously, if the virus is in human feces it must at least enter sewage, and the next epidemiologic query is How readily may it be demonstrated there?

A few investigations along both of these lines of approach will be reported in this paper. They include not only the use of the stool examination for the study of familial epidemiology in poliomyelitis but also some observations on the virus content of sewage.

TECHNIC OF STOOL EXAMINATIONS

Our procedures for the detection of the virus of poliomyelitis, together with the results of this type of examination on one hundred and eleven stools, are described in detail elsewhere.[6] Briefly, the method has consisted in the dilution of a relatively small specimen (15 to 25 Gm.) of feces with sterile water. To this suspension 15 per cent ether is added for bactericidal purposes, and the suspension is allowed to stand overnight. About 30 cc. of this suspension is centrifuged at moderate speed for half an hour and from 12 to 20 cc. of the middle layer is then injected intraperitoneally into one or more monkeys. The most important aspect of the test, however, has been the subsequent care of the inoculated monkeys. Daily temperature and exercise records have been kept on these animals for a period of four weeks, unless it seemed advisable to kill them earlier. If any monkey showed signs either definite or suggestive of poliomyelitis it was killed at what seemed an appropriate time. Histologic sections were examined from the medulla and from the cervical, thoracic and lumbar regions of the spinal cord of all killed monkeys, and if there were indications of poliomyelitis an immediate attempt was made to pass the virus to another monkey. If an animal died during the four weeks of observation from some cause other than poliomyelitis, the test was considered unsatisfactory. In the series of stool tests reported in this paper, premature deaths of the inoculated animals were, unfortunately, unusually frequent; among 31 inoculated monkeys it occurred ten times. Criteria for a positive result will be taken up later in this report under the section which deals with the detection of the virus of poliomyelitis in sewage.[6a]

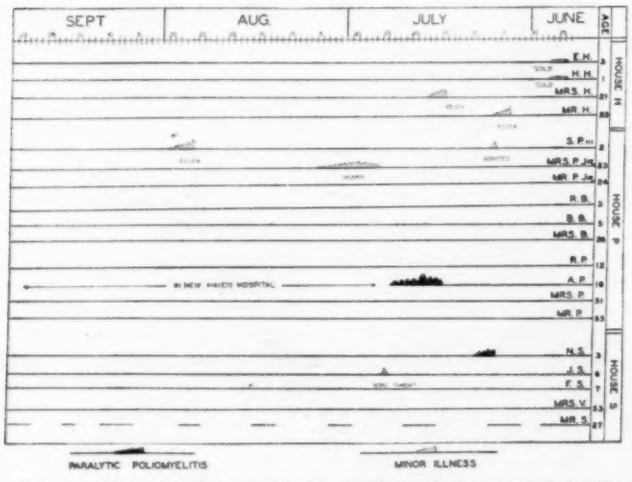

Fig. 1.—Schematic diagram of the members of six exposed families who lived in three houses. Each of the nineteen persons is designated by a horizontal line; the ages appear at the right. Legends on these lines mark the onset, duration and type of the various illnesses which occurred among this group during the summer of 1939.

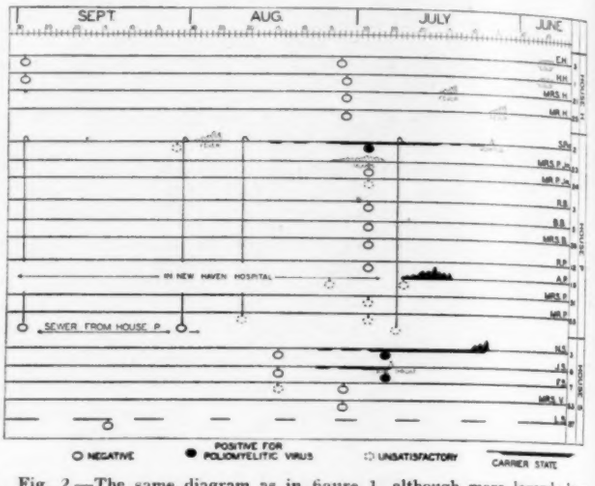

Fig. 2.—The same diagram as in figure 1, although more legends have been added indicating the results of stool tests and the estimated periods during which some of the children were intestinal carriers of the virus of poliomyelitis. Tests made on sewage taken from house P. are also shown.

CLINICAL OR FAMILIAL OBSERVATIONS

The present report describes the use of stool tests among a small group of persons during a rural epidemic in western Connecticut which occurred in the summer of 1939. Attention was first called to this situation in mid-July when A. P., a girl aged 18 years, was admitted to the New Haven Hospital with severe paralytic poliomyelitis. She came from a farm in rural Connecticut and was the first patient with the disease to be reported from that part of the state. Another patient with recent acute paralysis (N. S., aged 3 years) was soon discovered in the same community, and presently it became apparent that all the members of six related families who lived in three houses there had been exposed. This group was composed of nineteen persons, and besides the two with paralytic poliomyelitis there were several others who had acquired minor illnesses during late June and early July. The clinical events are best shown in the form of a diagram which gives the composition of the group and relates the various illnesses one to another in point of time (fig. 1).

Two of the patients with minor illnesses (Mr. and Mrs. H.) had symptoms compatible with those of abor-

5. Kramer, S. D.; Gilliam, A. G., and Molner, J. G.: Recovery of the Virus of Poliomyelitis from the Stools of Healthy Contacts in an Institutional Outbreak, Pub. Health Rep. **54**: 1914 (Oct. 27) 1939.

6. Trask, J. D.; Paul, J. R., and Vignec, A. J.: Poliomyelitic Virus in Human Stools, J. Exper. Med. **71**: 751 (June) 1940.

6a. Since this paper was written, Howe and Bodian (Untreated Human Stools as a Source of Poliomyelitis Virus, J. Infect. Dis. **66**: 198 [May-June] 1940) have found it advantageous to use nasal instillations of unetherized fecal suspensions for detecting virus in stools. This we have corroborated in a small series tested during the summer of 1940. At present we use both the intranasal instillation of fresh stool suspension and the intraperitoneal inoculation of centrifugalized, etherized material. Monkeys thus inoculated require at least five weeks of observation, instead of four.

tive poliomyelitis,[7] namely fever, headache and malaise of two or three days' duration. In some of the other cases the symptoms were equivocal; one was a case of mumps (the last of an epidemic of this disease which had been present in one of the three households for some weeks).

To unravel this complex situation we set out to determine by stool tests how many cases of poliomyelitis could actually be detected in this group, how many carriers (either convalescent or healthy) could be detected and whether these facts could be integrated so far as the manner of spread of the disease in this group was concerned. In securing the necessary material we were fairly though not completely successful, for during late July and early August, 19 stool specimens were obtained from 18 of the persons mentioned; a few more specimens were secured later in the summer. The whole series of tests totaled thirty-one. An unfortunate shortage of monkeys during July and August made it necessary to pool many of these specimens, so that material from 2 or 3 persons often went into 1 monkey, and if this animal came down, tests were then made on the individual specimens.

The clinical circumstances under which each specimen was obtained appear in figure 2. Here it will be seen that the first stool giving a positive result was from the 3 year old child N. S. (the first patient with paralysis in the epidemic), who had reached the twenty-first day of her disease when the first specimen of her stool was obtained. Later, on the thirty-ninth day of her disease, her stool specimen was normal. The next stool positive for poliomyelitis was from J. S. (the brother of N. S.), whose illness was mild, and without this laboratory finding one would have been inclined to regard his sore throat and slight fever as trivial. On the second day of this illness his stool contained the virus; later, on the twenty-first day, it was normal. The third patient whose stool gave positive laboratory evidence was a 2 year old boy, S. P. (the nephew of the 18 year old girl A. P.). He gave no definite history of a preceding illness except an attack of vomiting three

Fig. 3.—Map indicating the location of the building project downstream from house P.

weeks before. It is a question whether this indicates that the infant was a convalescent carrier early in the fourth week of his disease or a healthy carrier of unknown duration, such as those recently described by Kramer, Gilliam and Molner.[5] The distinction between the two would indeed be slight. Arbitrarily, however, we have called him a convalescent carrier.

A glance at figure 2 indicates that besides the 2 paralytic patients (N. S. and A. P.) and the 2 adults with probable abortive poliomyelitis (Mr. and Mrs. H.) identified on the basis of symptoms, the minor illness of J. S. also turns out to be abortive poliomyelitis, and there is perhaps still another if we include S. P. These last 2 are diagnosed on the basis of laboratory findings. This gives a total of 5 or 6 cases, and we find that they occurred in three groups so far as their date of origin is concerned. Two (or 3) began on July 3 and 7, 2 on July 14 and 1 on July 24, giving three waves of illness separated by intervals of about ten days—which is the usual average incubation time given for poliomyelitis. The first 2 patients (N. S. and Mr. H.) may well have been exposed simultaneously to the same unknown source. This is plausible because the entire H. family together with the first patient (A. P.) was visiting in house S. during the last of June. Most of the subsequent cases possibly might have resulted from the same exposure, but it seems more reasonable to regard them as secondary and tertiary cases.

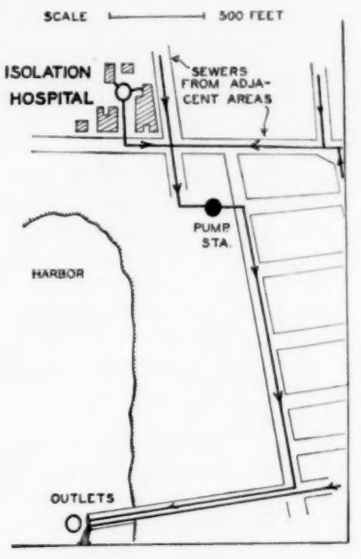

Fig. 4.—Map of the southwestern corner of the state of Connecticut on which are marked all cases of poliomyelitis (19) which were reported from the western third of the state in 1939. In July there was only 1 case (A. P.), for the illnesses of N. S. and S. P. were not reported to the state department of health as definite cases of poliomyelitis. The broken line pointing to the city of Waterbury indicates a possible association between the July case (A. P.) and one of the Waterbury cases (C. G.). The distribution of the cases along the Naugatuck River and the progression of the epidemic down the river are noteworthy.

Up to this point this epidemic was a family affair, but subsequently the epidemic took a different turn. On the basis of the reports to the state department of health, there was a case about this time in Bristol and there were 3 cases in Waterbury, to be followed by 14 more cases from the western third of Connecticut. Their geographic relationship to the small focus of cases in Waterbury and their riverside distribution is shown in figure 3. Most of the patients were admitted to the New Haven Hospital and most of their families were interviewed by us. In but 2 of the cases was there any history of association with the P. farm. This distributional relationship which the epidemic bore to the Naugatuck River (which drains off sewage and industrial waste from the city of Waterbury) implied that some factor existed in this epidemic which had to do with this watercourse. River epidemics like this one are not new or unique. Attention has been called to them in Sweden, Germany and Rumania by Kling,[8]

7. The terminology used for clinical poliomyelitis has been subject to frequent revision. Three terms are used here: paralytic poliomyelitis, abortive poliomyelitis and minor illness. The term minor illness is used in a special sense. It is applied here to those brief illnesses which occur so commonly among children during an epidemic of poliomyelitis, and it may be synonomous with the term suspected abortive poliomyelitis. Such minor illnesses may actually turn out to be abortive poliomyelitis, but at present they can be identified with certainty only if the virus of poliomyelitis is isolated from the patient.

8. Kling, C.: Recherches sur l'épidémiologie de la poliomyélite, Acta Soc. Med. Suecanae **55**: 23, 1929.

but they have received little notice of late in this country, although Caverly[9] in 1894 described his classic epidemic as being largely restricted to the Otter River valley of Rutland County, Vt. No explanation is, however, offered as to the part that watercourses may actually play in spreading the disease. Tests of water from the Naugatuck River for virus in this epidemic were not made.[9a] Nevertheless, from tests made elsewhere during the summer of 1939 it has become apparent that the virus of poliomyelitis may be present in sewage and that it may be transported for short distances by flowing sewage.

THE VIRUS OF POLIOMYELITIS IN SEWAGE

During the summer of 1939 there were several opportunities to study the natural presence of the virus of poliomyelitis in sewers during three large urban epidemics, viz. in Charleston, S. C., in Detroit and in Buffalo.[10] Our experiences so far as the positive results are concerned will be briefly described here.

Primarily a few more words about the technical procedures and the interpretation of the tests are again necessary. The method for examining sewage for the virus of poliomyelitis is based essentially on that used in examination of the stool. It has been described in more detail in another paper.[11] Samples of sewage (usually amounting to 4 liters) were collected in the morning. The specimens were allowed to settle for about two hours or longer and the supernatant fluid was then discarded. To the mid-layer (amounting to about 750 cc.) 10 to 15 per cent ether was added. The etherized specimens were transported (usually by airplane) to our laboratory in New Haven, and usually the day after their collection a dose of about 20 cc. was injected intraperitoneally into 1 or more rhesus monkeys. These animals were subsequently followed in the manner described under stool tests.

Results of Tests on Sewage from Hospital K, Showing the Number of Inmates with Poliomyelitis at the Time of Each Test

Date	Poliomyelitis Virus in Hospital Sewer	No. of Hospitalized Patients with Poliomyelitis
August 10	+	37
August 16	+	55
September 7	+	33
October 19	—	9
November 23	—	3

IDENTIFICATION OF THE VIRUS

One of the first questions that invariably arises when claims are made that the virus of poliomyelitis has been isolated from any unusual or extraneural source is How certain is it that it is the virus of poliomyelitis? Criteria on which the answer to this question is based will probably change from year to year, but those which we have used to define a positive result from sewage or stools are that the strain must fulfil at least three qualifications: 1. It must produce a "clinical picture" in the inoculated monkey which is compatible with that of experimental poliomyelitis, viz. after an appropriate incubation period a train of characteristic symptoms develops usually exemplified by fever, excitement, tremor, ataxia, weakness and paralysis, the latter being generally associated with a fall in temperature. 2. When the animal is killed, lesions typical of experimental poliomyelitis must be found in the region of the gray matter of the spinal cord, in lumbar as well as in cervical levels. These lesions should be "unequivocal," and besides their presenting evidence of neuronophagia there must be perivascular infiltrations with mononuclear cells. 3. Passage of the strain to a second monkey must be successfully accomplished, in the course of which criteria 1 and 2 must again be fulfilled. A fourth criterion is also valuable. It was used in almost all the sewage strains and consists in the injection of the strain (or the suspected material) into small laboratory animals such as rabbits, guinea pigs and mice. These animals should not acquire encephalomyelitis as a result of this inoculation. This last test should be helpful in differentiating the virus of poliomyelitis from that of lymphocytic choriomeningitis, equine encephalomyelitis and other viruses capable of producing an encephalitis or myelitis in these species, but it may be mentioned here that we have never succeeded in isolating from sewage any neurotropic virus other than that of poliomyelitis.

POSITIVE TESTS IN URBAN SEWAGE

During the summer of 1939, sixty-six tests were made on sewage collected in the course of the three urban epidemics just mentioned. Of these, thirteen were unsatisfactory, forty-five gave negative results, one gave a questionable result, and six gave positive results in that the three criteria were met, and one was positive so far as it went, for only the first two criteria were tried. The six giving positive results represented 4 different samples of sewage from two different sites. A strain from each of these 4 samples from the two sites fulfilled all four of the diagnostic criteria which we have considered useful in the identification of the virus of poliomyelitis.

In general the circumstances under which these few positive and many negative results were obtained indicated that it has been easier to isolate the virus of poliomyelitis from sewage collected in the vicinity of hospitals with poliomyelitic patients as inmates than from that gathered elsewhere. In the table five tests are recorded on sewage from one of the isolation hospitals in the city of Detroit. These tests were made on samples collected from a sewer pipe in the basement of the isolation building. The specimens here obtained on five occasions consisted of moderately cloudy or soapy water with a sediment of dark particles. Fecal material was not recognized as such grossly, but in spite of this "unpromising" looking material the virus was found repeatedly in this site. The relationship of the positive tests to the contemporaneous hospital populations appears in the table.

Besides the fact that the virus may be present in sewage, two other facts were determined: (*a*) that the total content of the virus of poliomyelitis in sewage may be large and (*b*) that the virus is stable enough to be transported by sewage for at least an eighth of a mile. Both of these facts were ascertained from tests[12] made

9. Caverly, C. S.: Preliminary Report on an Epidemic of Paralytic Disease Occurring in Vermont, in the Summer of 1894, Yale M. J. **1**: 1 (Nov.) 1894.

9a. Since this article was written we have had occasion to follow another small local epidemic of poliomyelitis which occurred during the summer of 1940. Again it was more or less restricted to this same river valley. During the epidemic period a few tests of the river water, which was heavily contaminated with sewage, were made. Poliomyelitis virus was not detected.

10. Dr. Leon Banov, health officer of Charleston; Dr. H. F. Vaughan, commissioner of health, Detroit, and Dr. F. E. Fronczak, health commissioner, Buffalo, gave permission for these studies. These health officers and the members of their staffs, and also Mr. G. E. Symons of the Buffalo Sewer Authority, assisted in this work.

11. Paul, J. R.; Trask, J. D., and Gard, Sven: Poliomyelitic Virus in Urban Sewage, J. Exper. Med. **71**: 765 (June) 1940.

12. Brief details of these tests are recorded in a preliminary note (Paul, J. R.; Trask, J. D., and Culotta, C. S.: Poliomyelitic Virus in Sewage, Science **90**: 258 [Sept. 15] 1939).

from a pumping station in Charleston, S. C., during the recent epidemic there which lasted from April through July 1939. The circumstances are best shown by a diagram of the sewage system in the immediate vicinity of the pumping station where this positive specimen was secured in mid-July (fig. 4). (Negative specimens were obtained from this site in early August and in October.) Two monkeys were inoculated intraperitoneally with this material in doses of 120 and 125 cc. respectively. In both of these animals poliomyelitis developed, and later a third monkey was infected with a concentrate made from 100 cc. of the same specimen.[13] Large as these three doses might have been, they were but "drops in the bucket" compared to the total volume of sewage pouring through this station, estimated at the rate of 470 gallons per minute. Theoretically, then, one could calculate that more than eighteen thousand doses of the virus of poliomyelitis infective for the monkey were passing through this site each minute of the hour in which the specimen was collected.

But of equal importance to the amount of virus in this large volume of sewage is the question of the source of the virus. If one assumes that this virus was of human origin, it then follows that it must have come either from patients in the isolation hospital or from patients or carriers in adjacent areas of the city (fig. 4) or from both. One conclusion that can be drawn from the positive finding is that whether or not the virus came from the hospital it seems to have survived in an urban sewerage system long enough to be transported for a distance of at least an eighth of a mile.

Other tests of sewage from this site which gave negative results are described in another publication. We did not succeed in isolating the virus from the many specimens collected after the major part of any of the epidemics was over.[13a]

COMMENT AND SUMMARY

From these laboratory experiences it appears that newer methods of testing human feces and sewage have been of assistance in detecting the existence of the virus of poliomyelitis throughout an infected community during epidemic times. An example of this type of assistance is illustrated by tests on some of the patients in an epidemic in rural Connecticut. At the onset of this epidemic, the cases were confined within a relatively small area, and stool specimens were obtained from persons who were thought to have been intimately exposed. Subsequently the epidemic became more scattered, and in its spread attention has been attracted to a fairly large polluted watercourse along which some of the patients seem to have been grouped.

During that summer, river and harbor water and large volumes of sewage were tested in three urban epidemics which occurred elsewhere in the country. From these samples, tested during epidemic times, the virus of poliomyelitis was detected in two sewers both of which were in the vicinity of hospitals, and from these tests we learned that not only can the virus content of sewage be large but the virus may be transported, for short distances at least, by flowing sewage.

It would seem unwise at present to make general statements about this finding so far as the epidemiology of poliomyelitis is concerned. We believe, as do others, that poliomyelitis is probably transmitted from one person to another by a number of different channels. Among these is the direct or indirect factor of close and intimate contact between infected persons, illustrated by the type of interfamilial contact in which juvenile members of a family usually share. Many of these infected persons may be convalescent carriers in the first few weeks of their recovery from either a diagnosed or a missed case; some of the exposed persons may become transient "healthy" carriers. But theoretically there may also be a variety of other channels in which contaminated food, milk and water, or conceivably insects, mammals or birds, play a part. That watercourses, and particularly watercourses polluted with sewage, may be related to one of these channels is suspected. The virus of poliomyelitis has never been isolated from "running water," but the tests herein reported show that it has been repeatedly isolated from "running" sewage. It is not evident from this last finding whether its presence in sewage is a direct or even an indirect link in the chain which leads this potentially infectious agent from one patient to another in this disease. Our observations merely call attention to in fact that the virus is there during epidemics.

789 Howard Avenue.

ABSTRACT OF DISCUSSION

DR. JAMES P. LEAKE, Washington, D. C.: The technic of Drs. Paul and Trask is the most important tool which has been developed for the epidemiologic study of poliomyelitis in years. They claim no originality, but they do deserve the credit. The high quality of their work on poliomyelitis is almost unique. It is only on the interpretation that there can be valid difference of opinion. I was glad to hear Dr. Trask say that in their study of clinical epidemiology it has seemed that what we ordinarily mean as human contact is that it is a method of transmission, by and large. One would infer from their figures that it is in the relatively young, and in those who have not in previous years acquired immunity to poliomyelitis, that we are most likely to have dangerous persons, dangerous in spreading the disease, and that is exactly the conclusion drawn from a study of the broad behavior of the disease in the United States over many years. Though their figures are small, they also tend to point to the nonparalytic and usually unrecognized case as being a more potent spreader of the disease than the recognized paralytic case. The general study of the disease apart from the authors' more exact study makes this obvious also. It is not clear to me, however, that healthy carriers may not be even more important than the nonparalytic or abortive or unrecognized cases of the disease. According to Trask, Paul and Vignette's published figures, about 15 per cent of their early cases were positive. They got this from the stools. From the fact that no positives were found among eight healthy contacts examined, one could say only that the incidence among such healthy contacts was less than 6 per cent. If such contacts for sampling were chosen among those who might have brought poliomyelitis into the family, they may have ceased to become carriers before the sample was taken. How does the virus get into the stools? That is a far different question from how the virus gets from one human body into another one. It seems to me it might well be that the virus might have been swallowed from nasopharyngeal secretions and discharged into the feces.

DR. T. M. RIVERS, New York: In spite of the good work that has been done, many questions regarding poliomyelitis remain unanswered. Indeed, there is no accurate yardstick whereby one can say that an individual case of illness is surely poliomyelitis and that an individual strain of virus unquestionably belongs in the poliomyelitic group. In addition, the matter of the portal of entry of virus in man and how the virus spreads

13. Gard, Sven: A Method for Detecting Poliomyelitic Virus in Sewage and Stools, J. Exper. Med. **71**: 779 (June) 1940.

13a. During an epidemic of about 70 cases of poliomyelitis which occurred in Stockholm, Sweden, in the fall of 1939, Kling also was successful in isolating poliomyelitis virus from the local sewage (Levaditi, C.: Sur la présence du virus poliomyélitique dans les eaux d'égout, Bull. Acad. de méd., Paris **123**: 335 [April 23-30] 1940). In our second series of sewage tests, carried on during the summer of 1940, a single positive result was obtained from a large sewer in New York City, which was not in the vicinity of an isolation hospital, although cases of poliomyelitis were present within the area this sewer drained.

from man to man in nature are not clear; furthermore, there is an amazing lack of knowledge regarding the pathology of human poliomyelitis in relation to the idea of axonal transmission of the virus. All these questions are being vigorously attacked at the present time by a number of investigators. I should like to ask Drs. Paul and Trask two questions: Why is it that specimens of stools injected into the peritoneal cavity of monkeys bring them down with poliomyelitis in such a high percentage of cases, when fresh brain material full of active virus does not bring them down? How many instances of virus in the stool are they missing? We know that they have found it in a certain percentage of the cases and, if I am not mistaken, the percentage must be considerably higher than they have found.

DR. HAROLD L. AMOSS, Greenwich, Conn.: The investigation of poliomyelitis may be divided into three periods: 1. The clinical and field studies of the previrus era, represented by the studies of Caverly and Wickman, pointed to the concept of dissemination of the virus through direct contact but more largely through persons with mild, abortive or subclinical forms of the disease. 2. The second period, initiated by the transmission of the disease to monkeys by Landsteiner and Popper, and the work of Flexner and Lewis, began a period of investigation which centered on the virus itself and the behavior of the experimental disease. The results of these studies were corroboration of the essential concept arrived at by the earlier studies, and then the implication of the nasal mucosa, or other barriers to the central nervous system, as determinants of clinical or subclinical infection on exposure to the virus. Later the application of the neutralization test for serologic immunity in epidemiologic studies revealed a process of immunization in the general population taking place to the same extent and with the same rapidity as with the more common widespread infectious agents, such as measles and diphtheria. Thus the concept of widespread dissemination of the virus, with limited occurrence of the paralytic disease, has held through the whole period of investigation. It has received corroboration and gained in stature at each additional step; furthermore, it has withstood the challenge of innumerable opposing theories. But this trend in thought and investigation has at no time been seriously, or for long, set aside. Many theories, on the surface more plausible, have been eagerly grasped and have had their day, only to fail when put to test or when further investigation has forced us back to the concept which now stands highest because of the support of valid, consistent observations. 3. In the first two periods the emphasis was placed on the virus itself, or exposure to the virus as the major factor in the determination of disease distribution, and the mode of spread of the virus was the central idea in epidemiologic studies. A third period, marked by the acceptance of widespread dissemination of the virus and a shift of emphasis from the mode of spread of the virus itself to the epidemiologic studies of the paralytic disease among those exposed, is represented by the trend of researches of the present and has further developed the idea that the occurrence of the paralytic disease among those exposed to the virus not only is limited but exhibits certain selectivities. These selectivities point not so much to factors of exposure as to factors in the exposed as a major determinant of the paralytic disease. The implications are that a disturbance of the intact mucous membrane during harborage of the virus is an etiologic factor in the disease.

DR. JAMES D. TRASK, New Haven, Conn.: Dr. Rivers asked us two questions. The first one is How many times did we miss finding the virus in stools? I think that this may have happened frequently. In the spring of 1939 Dr. McClure, of Albany, detected virus in the stools of five children during a small outbreak in Syracuse. Two days after him we collected stools from the same children and our tests were negative with all five. The second question of Dr. Rivers is Why does intraperitoneal inoculation of stool succeed when passage of monkey cord generally must be done intracerebrally? We think that the reason is that the spinal cord of inoculated monkeys frequently contains antibodies for the virus together with the virus. Thus as in the case with mixtures of antibodies and virus in other diseases (vaccinia, for example) passage may succeed with the intracerebral route when the subcutaneous or intraperitoneal routes may fail.

Clinical Notes, Suggestions and New Instruments

SIGNIFICANCE OF HEMORRHAGIC TAP IN APOPLEXY

A. H. TERRY JR., M.D.; SIGMUND FALK, M.D., AND L. H. BRONSTEIN, M.D., NEW YORK

At one of the clinical conferences at the Beekman Street Hospital an intern unwittingly provided the stimulus for this paper, stating that he had never seen a patient recover who had a cerebral hemorrhage associated with a hemorrhagic or bloody spinal fluid. This started the ball rolling. Every one had a foggy prognostic idea but no one was sufficiently wise to settle the question. A search of the literature for the last ten years, as well as a review of the standard textbooks of pathology and neurology, failed to provide the answer. If the subject was touched on at all, a single statement that this was a poor sign was the sole conclusion—how poor a sign was never stated. The original articles in the literature safely attacked the problem from hindsight, analyzing autopsy material. Such studies disclosed that in cases coming to autopsy cerebral hemorrhages had a shorter existence when there was rupture into the ventricles. This showed which way the wind blew after the ship was wrecked but provided no barograph to protect the medical mariner against the force of the storm when it struck. Our desire was primarily to know what prognosis to give patients admitted to the hospital, after cerebral accidents, with sanguineous spinal fluid. We undertook to eliminate vascular damage occurring at the base of the brain and confine ourselves to cases due to hemorrhage or thrombosis in the brain, commonly referred to as "apoplexy," "stroke" or "shock." We reviewed 173 such cases, and the results are here tabulated. The spinal fluid is referred to as bloody, slightly bloody, xanthochromic or clear. Sometimes there was no tap because the patient was too sick or too well or because the procedure did not meet with the approval of the attending physician. The length of survival is given in hours, days and weeks.

Results in 173 Cases of Hemorrhage or Thrombosis of the Brain

	Hours				Hospital Days						Weeks		Survived	Died	Total
Type Fluid	1-2	2-6	6-12	12-24	2	3	4	5	6	7	2d	3d			
Bloody	8	11	5	3	4	3	2	1	1	..	3	..	2	41	43
Slightly bloody	..	1	..	2	1	1	1	2	1	..	..	1	2	10	12
Xanthochromic	..	1	1	..	..	1	..	..	..	..	1	..	3	4	7
Clear tap	1	..	2	6	2	..	5	1	1	2	2	..	20	22	42
No tap	5	16	6	3	5	5	1	3	1	2	2	..	20	49	69
Total													47	126	173

SUMMARY

1. Of 173 patients with cerebral hemorrhage or thrombosis, 47 (27 per cent) survived.

2. If there was hemorrhagic spinal fluid, 2 (less than 5 per cent) survived.

3. If there was slightly hemorrhagic spinal fluid, 2 (16 per cent) survived.

4. If there was clear tap, 20 out of 42 (about 48 per cent) survived.

5. When no tap was done, 20 out of 49 (40 per cent) survived.

COMMENT

No attempt is made to evaluate these statistics beyond satisfying the original question. All were hospital cases, perhaps worse than the regular run of the mill but nevertheless more illuminating than none at all, and they provide some kind of an answer to an incredulous hospital intern, and so to him the conclusion is that cases of apoplexy presenting hemorrhagic spinal fluid are 95 per cent fatal.

From the Beekman Street Hospital.

SCLERODERMA WITH PULMONARY FIBROSIS

JOHN R. MURPHY, M.D.; PHILIP KRAININ, M.D., AND MARTIN J. GERSON, M.D., NEW YORK

The pathologic changes in diffuse scleroderma are not confined to skin and subcutaneous tissue alone but involve the connective tissue system throughout the entire body. Muscle, fascia, tendon, bone and at times even the endocrine glands and the internal organs participate in the disease process. Everywhere the same changes occur, namely edema followed by sclerosis of the collagenous bundles. This may occur in the connective tissue between the alveoli of the lung, the acini of the liver, the glomeruli of the kidney and the muscle fibers of the heart and within the pulp of the spleen.[1] The smaller arteries within the regions involved show corresponding sclerotic degeneration and thickening of the intima which may proceed to obliteration of the lumen and subsequent focal necrosis.[2]

The case to be presented is of interest because it has been possible to demonstrate visceral pathologic changes, namely pulmonary fibrosis or sclerosis as a clinical manifestation. A search of the literature of scleroderma has brought to light no other case in which the pulmonary manfestations of the disease were visualized by roentgenographic study.

REPORT OF CASE

History.—D. M., a Southern Negress aged 30, a housewife, entered the Morrisania City Hospital May 4, 1939, complaining of gradual loss of weight and a feeling of discomfort in the chest. During the past six months her weight had dropped from 115 to 102 pounds (52 to 46 Kg.). Since February she had noticed stiffness of her fingers and aching pains in her shoulders and arms. There was occasional cough, with expectoration of

Fig. 1.—Appearance of patient, showing sclerodactyly and masklike facies.

a small quantity of thin mucoid sputum, never blood streaked. In March she noted a tightening of the skin of her face and a thickening of the skin over her hands, forearms and legs. Shortly before admission she began to complain of some difficulty in breathing because of a sensation of "tightness in the chest."

The past history revealed no illnesses; she had not had pneumonia, pleurisy or frequent colds. For at least five years there had been a painless deformity of the finger tips and nails. The menses were regular, with onset at 12 years, of three days' duration. The menstrual flow had been scanty during the six

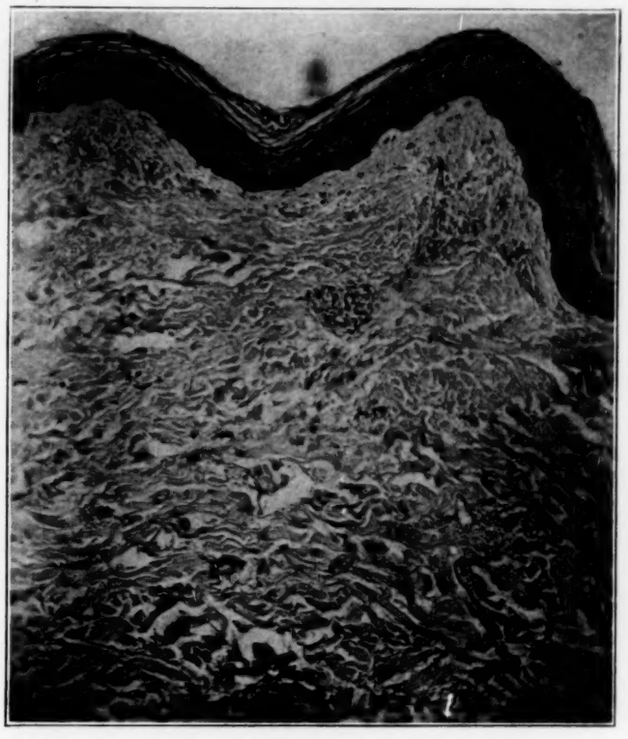

Fig. 2.—Section of epidermis and corium of patient with scleroderma (low power magnification).

months prior to admission. Her two children, 7 and 12 years of age, were living and well; there had been one miscarriage at two months. Both her parents had died late in life of pneumonia.

Examination.—The patient was poorly nourished, tall and thin, and not dyspneic or orthopneic. The facies was masklike and devoid of wrinkles and furrows (fig. 1). The skin of the face, arms and forearms, legs and feet was thickened and shiny; it was difficult to raise a fold of skin from these sites. Areas of mottled depigmentation were present over the nose, about the mouth and chin and on the anterior aspect of both legs. The thickening of the skin over the chest and abdomen was less obvious. The hands and feet were cold to the touch. There was shortening of the fingers and a clubbing of the terminal phalanges. The nails presented longitudinal striae. There was no limitation of motion of the extremities.

The pupils were equal and regular and reacted to light and in accommodation. The media were clear and the fundi presented a normal appearance. There were no abnormalities in the mucous membranes of the nose, throat or mouth. The skin of the neck was minimally involved in the sclerodermatous process and was freely movable; no lymph nodes were palpable. The trachea was located in the midline and the thyroid was not enlarged. The anteroposterior diameter of the chest was not increased, but the excursion of the chest appeared to be limited on inspiration. Percussion resonance over the lungs was impaired with diminished breath sounds throughout. No rales could be heard. The heart was not enlarged. There was regular sinus rhythm and the sounds were of good quality. The second pulmonic sound was accentuated and there was a soft apical systolic murmur. Blood pressure was 100 mg. systolic and 65 mg. diastolic. The abdomen was moderately distended but soft. The tip of the spleen was palpable. No abnormalities

From the Medical Service of Dr. David Greenberg, Morrisania City Hospital.

1. Cassirer, Richard, and Hirschfeld, Robert: Die Sklerodermie, in Kraus, Fredrich, and Brugsch, Theodor: Spezielle Pathologie und Therapie innerer Krankheiten, Berlin, Urban & Schwarzenberg, 1924, vol. 10, pt. 3, p. 557.

2. Masugi, M., and Yä, S.: Die diffuse Sklerodermie und ihre Gefässveränderung, Virchows Arch. f. path. Anat. **302**: 39, 1938.

were found on rectal or vaginal examination. The reflexes were physiologic and no abnormal neurologic changes were elicited.

A piece of skin was removed from the anterior aspect of the left leg and examined microscopically. The epidermis was of normal thickness with dense pigmentation present in the malpighian layer. The dermal papillae were flattened and indistinguishable from the remainder of the corium, which consisted of thick coarse bundles of collagenous fibers intertwining in all directions and containing few cellular elements. There was a marked increase in the thickness of the corium, the result of connective tissue sclerosis. Few small blood vessels were to be seen. There was a paucity of hair follicles and sweat glands. The subcutaneous fatty layer was much thinner than usual (fig. 2).

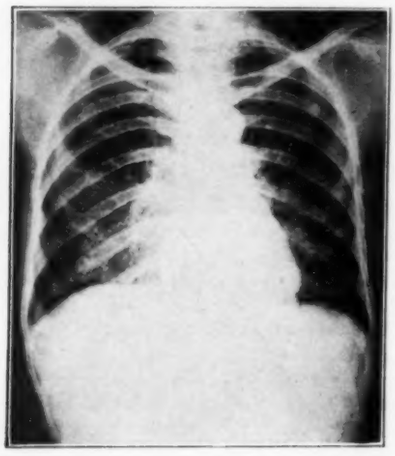

Fig. 3.—Appearance of chest, showing pulmonary fibrosis.

Roentgenographic examination of the chest showed no abnormality of the ribs or of the diaphragm, and the heart appeared within normal limits of size and shape. Within both pulmonary fields, exclusive of the apexes and the lateral aspect of the bases, there was a diffuse network-like shadow extending from the cardiac border to the periphery. This shadow was dense in the lower halves of the lung fields but thinned out and became strandlike in the subclavicular regions (fig. 3). Bronchography with iodized poppyseed oil was performed, and this revealed a normal bronchial tree.

Except for small fragments of residual bone, the distal phalanges of the hands were absent and there was partial destruction of the distal half of the terminal phalanges of each fifth toe. The long bones were normal. There was a slight cloudiness of the left maxillary antrum.

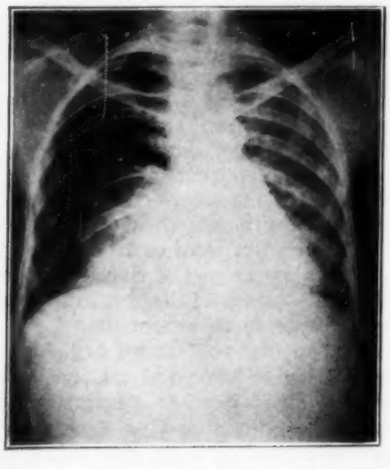

Fig. 4.—Appearance of chest after right pneumothorax. Note absence of markings in the right side of the chest.

An electrocardiogram revealed only left axis deviation.

Examination of the blood showed 11,000 leukocytes, of which 68 per cent were polymorphonuclears, 31 per cent lymphocytes and 1 per cent monocytes. There were 5.5 million erythrocytes with 78 per cent hemoglobin. The Kahn reaction of the blood was negative. Chemical examination revealed a serum calcium of 10 mg. per hundred cubic centimeters and again 10.1 mg., and a serum phosphorus of 4.5 mg. per hundred cubic centimeters. Serum phosphatase was 5.4 Bodansky units.

Serum cholesterol was 229 mg. per hundred cubic centimeters on one occasion and 200 mg. on another. Urea nitrogen was 7.2 mg. and dextrose 107 mg. per hundred cubic centimeters.

Venous pressure was equivalent to 7.5 cm. of water, and the circulation time was 7 seconds for ether and 15 seconds for saccharin.

The sputum was repeatedly negative for tubercle bacilli and a tuberculin test in the dilution of 1:10,000 gave negative results. The urine was normal and the basal metabolic rate was plus 11.

Course.—On the fifth day after admission the patient had a chill with a temperature of 105 F., together with swelling over the bridge of the nose. The lesion rapidly spread in butterfly fashion with a well defined border, so that within twenty-four hours the eyelids, forehead and cheeks were involved. The leukocyte count rose to 27,900 with 92 per cent polymorphonuclears. This was diagnosed as erysipelas. Sulfanilamide was administered and within forty-eight hours the temperature was normal and the facial swelling had almost completely disappeared.

During her stay in the hospital the patient gained weight, and the bone and joint pains disappeared. The sense of discomfort persisted but there was never any objective respiratory distress. She was discharged improved on August 2.

Because of the possibility that the pulmonary shadows viewed on the original roentgenograms might have been caused by sclerosis of the overlying skin and muscle, a diagnostic pneumothorax was performed on the right side and partial collapse was obtained. Check-up films revealed that the pathologic changes previously observed were caused by a lesion within the lung and the appearance of fibrosis was not demonstrable in the soft tissues of the chest wall (fig. 4).

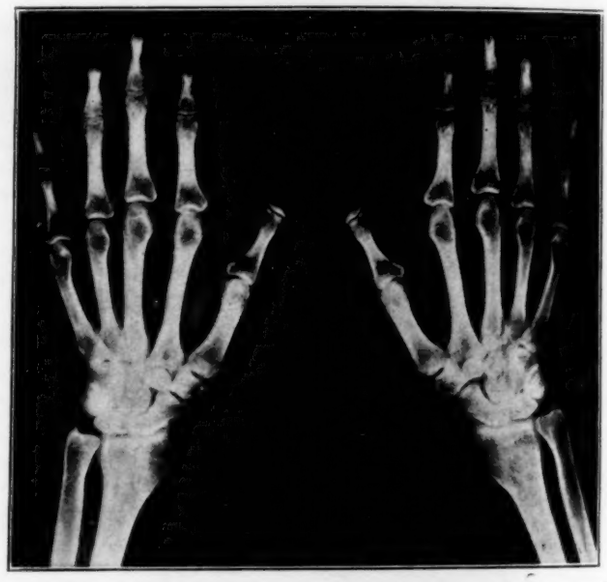

Fig. 5.—Appearance of hands, showing almost complete absence of distal phalanges.

COMMENT

One may read many protocols of autopsies in which scleroderma was seen without finding reference to pathologic changes in the lungs other than incidental pneumonia, pleuritis, silicosis, tuberculosis and the like, all clearly unrelated to the disease process itself. Rarely, however, has a characteristic diffuse pulmonary fibrosis been described. The observers who have noted this are Notthafft,[3] Matsui[4] and Kraus,[5] with a total of six cases. There was a varying amount of pulmonary emphysema in each case associated with hypertrophy and dilatation of the right ventricle of the heart. Histologically, the appearance was that of a "chronic interstitial pneumonia" with extensive connective tissue proliferation and thickening of the alveolar septums, together with changes in the associated blood vessels. The arteries showed marked proliferation of the intima,

3. von Notthafft, Albrecht: Neuere Arbeiten über Sklerodermie, Centralbl. f. allg. Path. u. path. Anat. **9**: 870 (Nov. 15) 1898.

4. Matsui, S.: Ueber die Pathologie und Pathogenese von Sklerodermia universalis, Mitt. a. d. med. Fak. d. k. Univ. zu Kyoto **31**: 55, 1924.

5. Kraus, E. J.: Zur Pathogenese der diffusen Sklerodermie, Virchows Arch. f. path. Anat. **253**: 710, 1924.

hypertrophy of the media and infiltration with round cells. Matsui called attention to the disturbance in the lesser circulation resulting from interference with the pulmonary vascular bed, producing right ventricular hypertrophy. Roentgenographic studies of the lungs were not made.

Our case showed no evidence of cor pulmonale. The cardiac shape, circulation time and venous pressure were normal and the electrocardiogram showed left axis deviation. We feel justified in attributing the pulmonary changes viewed on the x-ray films[6] to the sclerodermatous process, since there was no history of respiratory infections or exposure to dusts and since both bronchiectasis and tuberculosis could be excluded. The roentgenographic appearance of pulmonary fibrosis occurring in generalized scleroderma has never before been reported. Puddu,[7] however, described fine calcified areas scattered throughout both lungs, visualized on the x-ray films, in a case of Thibierge-Weissenbach syndrome (scleroderma with calcinosis).

121 East Sixty-First Street—9 Thayer Street.

Special Article

GLANDULAR PHYSIOLOGY AND THERAPY

THE ESTROGENIC SUBSTANCES

EDWARD A. DOISY, PH.D., D.Sc.
ST. LOUIS

This special article is published under the auspices of the Council on Pharmacy and Chemistry. It is one of a series which will be published in book form as the second edition of "Glandular Physiology and Therapy." The opinions expressed in these articles are those of the authors and not the official views of the Council.—ED.

Although several investigators[1] contributed to the early development of research on estrogens, rapid progress did not begin until after the publication of the vaginal smear reaction[2] for the detection of these substances. The work was given additional impetus by the discovery of the high concentration of estrogens in the urine of pregnant women and in the urine of pregnant mares.[3] These discoveries, which provided excellent sources of the estrogens and the means of quantitative determination, were of paramount importance to the isolation of the estrogens and the determination of their structure, as well as to the introduction of an ample supply of estrogenic substances for therapeutic use. The subsequent availability of pure estrogens has permitted an investigation of their role in sex physiology, particularly with respect to the estrous and the menstrual cycle, and of their interrelationships with other internal secretions.

6. Dr. Samuel Weitzner made the x-ray studies in this case.

7. Puddu, Vittorio: Un caso di sclerodermia con calcificazioni, Policlinico (sez. prat.) **41:** 1801 (Nov. 19) 1934.

From the Department of Biochemistry, St. Louis University School of Medicine.

1. Adler, L.: Zur Physiologie und Pathologie der Ovarialfunktion, Arch. f. Gynäk. **95:** 349, 1912. Fellner, O. O.: Experimentell erzeugte Wachstumsveränderungen am weiblichen Genitale der Kaninchen, Zentralbl. f. allg. Path. u. path. Anat. **23:** 673, 1912. Herrmann, E.: Ueber eine wirksame Substanz im Eierstocke und in der Placenta, Monatschr. f. Geburtsh. u. Gynäk. **41:** 1, 1915. Frank, R. T., and Rosenbloom, J.: Physiologically Active Substances Contained in the Placenta and in the Corpus Luteum, Surg., Gynec. & Obst. **21:** 646, 1915.

2. Allen, Edgar, and Doisy, E. A.: An Ovarian Hormone: Preliminary Report on Its Localization, Extraction and Partial Purification and Action in Test Animals, J. A. M. A. **81:** 819 (Sept. 8) 1923.

3. Aschheim, Selmar, and Zondek, Bernhard: Hypophysenvorderlappen Hormon und Ovarialhormon im Harm von Schwangeren, Klin. Wchnschr. **6:** 1322 (July 9) 1927. Zondek, Bernhard: Mass Excretion of Oestrogenic Hormone in the Urine of the Stallion, Nature, London **133:** 209 (Feb. 10) 1934.

CHEMISTRY OF ESTROGENIC SUBSTANCES

At this point a brief review of the chemistry of both the natural and the synthetic estrogens may prove valuable to the reader. According to a system of nomenclature proposed by a group of British investigators,[4] the parent saturated hydrocarbon is named estrane, and the unsaturated hydrocarbon from which the natural estrogens are derived, $\Delta^{1,3,5}$-estratriene. The first natural estrogen isolated in a crystalline form was named theelin by Doisy;[5] according to its relationship to estrane, it is 3-hydroxy-17-keto-$\Delta^{1,3,5}$-estratriene. For convenience this name has been abbreviated to estrone. The Council on Pharmacy and Chemistry of the American Medical Association recognizes as nonproprietary names both estrone and theelin.[6]

Natural and Synthetic Estrogens.—Estrone, or theelin, $C_{18}H_{22}O_2$, the first pure estrogen to be isolated, was obtained in 1929 from human pregnancy urine.[7] Later it was obtained in crystalline condition from the urines of pregnant mares, stallions and men, from human placenta, from adrenal glands (probably beef) and from palm kernels. Its presence in sow ovaries was clearly indicated by physical, chemical and physiologic reactions. A conjugated form, estrone sulfate, has been isolated from mare's urine.

Estriol, or theelol, $C_{18}H_{24}O_3$, is obtained from human pregnancy urine,[8] human placenta and pussy willows (?). A conjugated form, estriol glycuronide, has been isolated from human pregnancy urine. The relationship of estriol to estrone was established on conversion of the former to the latter by dehydration.

Estradiol, or dihydrotheelin, $C_{18}H_{24}O_2$, can be obtained by reduction of estrone in two isomeric forms, due to the new asymmetric carbon atom 17. The alpha compound has been isolated from sow ovaries,[9] the urine of pregnant mares, human pregnancy urine and human placenta. The beta form has also been obtained from mare's urine.

4. Adam, N. K.; Danielli, J. F.; Dodds, E. C.; King, H.; Marrian, G. F.; Parkes, A. S., and Rosenheim, O.: Nomenclature of the Oestrin Group, Nature, London **132:** 205 (Aug. 5) 1933.

5. Veler, C. D.; Thayer, S. A., and Doisy, E. A.: The Preparation of the Crystalline Follicular Ovarian Hormone: Theelin, J. Biol. Chem. **87:** 357 (June) 1930.

6. The Nomenclature of Estrus-Producing Compounds, Report of the Council on Pharmacy and Chemistry, J. A. M. A. **107:** 1221 (Oct. 10) 1936.

7. Doisy, E. A.; Veler, C. D., and Thayer, S. A.: Folliculin from the Urine of Pregnant Women, Am. J. Physiol. **90:** 329 (Oct.) 1929. Butenandt, Adolf: Ueber "Progynon" ein krystallisiertes weibliches Sexualhormon, Naturwissenschaften **17:** 878, 1929. de Jongh, S. E.; Kober, S., and Laqueur, Ernst: Ueber Identität des Brunsthormons (Menformon) aus Harn schwangerer Frauen und aus Harn trächtiger Pferde, Biochem. Ztschr. **240:** 247, 1931. Häussler, E. P.: Ueber das Vorkommen von α-Follikelhormon (3-oxy-17 keto-1,3,5-oestratriën) im Hengsturin, Helvet. chim. acta **17:** 531, 1934. Deulofeu, Venancio and Ferrari, J.: Krystallisiertes α-Follikelhormon aus Hengstharn, Ztschr. f. physiol. Chem. **226:** 192, 1934. Dingemanse, E.; Laqueur, Ernst, and Mühlbock, O.: Chemical Identification of Oestrone in Human Male Urine, Nature, London (supp.) **141:** 927 (May 21) 1938. Westerfeld, W. W.; MacCorquodale, D. W.; Thayer, S. A., and Doisy, E. A.: The Isolation of Theelin from Human Placenta, J. Biol. Chem. **126:** 195 (Nov.) 1938. Beall, D.: Isolation of Estrone from the Adrenal Gland, Nature, London **144:** 76 (July 8) 1939. Butenandt, Adolf, and Jacobi, H.: Ueber die Darstellung eines krystallisierten pflanzlichen Tokokinins (Thelykinins) und seine Identifizierung mit dem α-Follikelhormon, Ztschr. f. physiol. Chem. **218:** 104, 1933. Westerfeld, W. W.; Thayer, S. A.; MacCorquodale, D. W., and Doisy, E. A.: The Ketonic Estrogen of Sow Ovaries, J. Biol. Chem. **126:** 181 (Nov.) 1938. Schachter, Benjamin, and Marrian, G. F.: The Isolation of Estrone Sulfate from the Urine of Pregnant Mares, ibid. **126:** 663, 1938.

8. Marrian, G. F.: Observations on the Chemical Nature of Crystalline Oestrin, J. Soc. Chem. & Ind. **49:** 515, 1930. Doisy, E. A.; Thayer, S. A.; Levin, Louis, and Curtis, J. M.: A New Tri-Atomic Alcohol from the Urine of Pregnant Women, Proc. Soc. Exper. Biol. & Med. **28:** 88 (Oct.) 1930. Browne, J. S. L.: The Chemical and Physiological Properties of Crystalline Estrogenic Hormones, Canad. J. Research **8:** 180 (Feb.) 1933. Skarżyński, B.: An Oestrogenic Substance from Plant Material, Nature, London **131:** 766 (May 27) 1933. Cohen, S. L., and Marrian, G. F.: The Isolation and Identification of a Combined Form of Œstriol in Human Pregnancy Urine, Biochem. J. **30:** 57 (Jan.) 1936. Butenandt, Adolf, and Hildebrandt, F. M.: Ueber ein zweites Hormonkrystallisat aus Schwangerenharn und seine physiologischen und chemischen Beziehungen zum krystallisierten Follikelhormon, Ztschr. f. physiol. Chem. **199:** 243, 1931.

9. MacCorquodale, D. W.; Thayer, S. A., and Doisy, E. A.: The Isolation of the Principal Estrogenic Substance of Liquor Folliculi, J. Biol. Chem. **115:** 435 (Sept.) 1936. Wintersteiner, Oskar; Schwenk, Erwin, and Whitman, Bradley: Estrogenic Dihydroxy Compounds in Urine of Pregnant Mares, Proc. Soc. Exper. Biol. & Med. **32:** 1087 (April) 1935. Huffman, M. N.; MacCorquodale, D. W.; Thayer, S. A.; Doisy, E. A.; Smith, G. V., and Smith, O. W.: The Isolation of α-Dihydrotheelin from Human Pregnancy Urine, J. Biol. Chem. **134:** 591 (July) 1940. Huffman, M. N.; Thayer, S. A., and Doisy, E. A.: The Isolation of α-Dihydrotheelin from Human Placenta, ibid. **133:** 567, 1940.

Several other natural estrogens have been isolated. In 1932 three additional compounds, equilin, hippulin and equilenin,[10] were obtained from the urine of pregnant mares. Subsequently, Wintersteiner and his collaborators isolated α-estradiol, β-estradiol and α-dihydroequilenin from the same source.

Owing to the minute concentration of estrogen and the large quantity of lipid contaminants, the isolation of estrogens from solid tissues did not proceed so rapidly. In 1930 Browne obtained estriol from human placenta, but it was not until 1938 that theelin and not until 1940 that α-dihydrotheelin were obtained from that tissue. α-Dihydrotheelin was isolated from sow ovaries in 1935, and the existence of approximately an equal concentration (about 6 mg. per ton) of theelin in sow ovaries was demonstrated in 1938.

Owing to the effect of certain types of adrenal tumors on sexual development, the isolation of estrone from adrenal extracts is interesting. Is estrone formed normally in the adrenal? If so, is this purposeful production, or is the substance merely a by-product of the steroid syntheses which seem to occur so profusely in the adrenal?

The synthesis of equilenin from simple starting materials by Bachmann[11] is one of the great accomplishments of the chemist in the sex hormone field. Although partial syntheses have given progesterone and several androgens, the production of equilenin is the first total synthesis of a sex hormone.

In addition to the synthesis of the natural estrogen, equilenin, several compounds having estrogenic properties have been synthesized. The first compound which was prepared, 1-keto-1, 2, 3, 4-tetrahydrophenanthrene,[12] had relatively feeble activity, but finally compounds of exceptional potency were obtained. 9, 10-Dihydroxy-9, 10-di-n-propyl-9, 10-dihydro-1, 2, 5, 6-dibenzanthracene and triphenylethylene have a fair degree of activity, but stilbestrol and hexestrol have potencies of the same magnitude as estrone. Similar to the natural estrogens, stilbestrol and hexestrol have phenolic properties.

Chemical and Physical Properties of the Natural Estrogens.—Since all of the natural estrogens are phenolic and all other known sex hormones are not phenolic, a separation can readily be effected through the solubility of the former in aqueous alkali. The relative insolubility of the estrogens in purified petroleum benzine U. S. P. (petroleum ether) has been important in their separation from other lipids.

In all of the estrogens ring A is aromatic and, consequently, the hydroxyl on carbon atom 3 is phenolic. The only other point of substitution in the hydrocarbon structure is at carbon atom 17, at which either a carbonyl or a secondary alcohol is present. If the latter is present, two stereoisomers are possible, depending on the relative position of the hydroxyl.

Two reagents have been used successfully to separate the ketonic from the nonketonic estrogens. Trimethylaminoacethydrazide chloride (Girard and Sandulesco[13a]) and carboxymethoxylamine (Wintersteiner[13b]) react with ketonic estrogens to form water-soluble derivatives. In addition to the reactions with these reagents, the ketonic compounds react with hydroxylamine, semicarbazide, acetylene and the Grignard reagents.

The phenolic hydroxyl reacts with a variety of compounds to produce esters; perhaps the acetate and benzoate are the best known. The 3, 17 dihydroxy estrogens can be converted into 3, 17 diesters, the 3-monoester or the 17-monoester. Esters of these types with several different acids have been synthesized by Miescher and Scholz.[14] The 3 benzoate and 3, 17 dipropionate of α-estradiol are used therapeutically.

Like simple phenols, the estrogens give color reactions with Millon's reagent, diazotized aromatic amines and Folin's phenol reagent. In addition, Kober[15a] has shown that under certain conditions estrogens react with a mixture of phenol and sulfuric acid to give a red color, the intensity of which could be used for quantitative determinations. Cohen and Marrian[15b] proposed a method for the separation of estrone and estriol and determined the estrogen of each fraction by a modification of the Kober reaction. Additional modifications of the Kober reaction have been proposed by Bachman.[15c] Owing to the rapidity of execution and the accuracy of the results, it seems likely that in many instances these colorimetric analyses may displace determinations by bioassay.

The structure of the estrogens has been established through the contributions of several investigators. Butenandt, Weidlich and Thompson[16a] showed that rings A, B and C are fused together as in phenanthrene; Haworth and Sheldrick,[16b] that the hydroxyl in ring A is in the three position, and Cohen, Cook and Hewett,[16c] that the estrogens are perhydro derivatives of 1, 2-cyclopentenophenanthrene having the angle methyl group on carbon atom 13 and the oxygen atom on carbon atom 17. Confirmation of the accepted views of structure has been effected by the splendid synthetic work of Bachmann and co-workers,[11a] in which a simple compound, 1-naphthylamine-6-sulfonic acid, has been converted by a series of reactions into equilenin. Since the conversion of equilenin into estrone had already been described by Marker, the structures of both estrone and equilenin are fully established.

BIOLOGIC REACTIONS OF THE ESTROGENS

As Edgar Allen[17] pointed out in the first edition of "Glandular Physiology and Therapy," the estrogens are primarily growth-promoting agents. Certain of the more important reactions will be considered in some detail. Similar to the natural estrogens, the synthetic estrogen, stilbestrol, produces almost all, if not all, of the effects of the natural estrogens.

The Vaginal Reaction.—Early work on the ovariectomized rat and mouse showed that injections of estrogen were followed by growth of the vaginal epithelium, the thickness increasing from two or three to about fifteen cells.[18] The sloughing of squamous

10. Girard, André; Sandulesco, A.; Fridenson, A., and Rutgers, J. J.: Sur une nouvelle hormone sexuelle cristallisée retirée de l'urine des juments gravides, Compt. rend. Acad. d. sc. **194:** 909 (March 7) 1932; Sur une nouvelle hormone sexuelle cristallisée, ibid. **195:** 981 (Nov. 21) 1932. Hirschmann, H., and Wintersteiner, Oskar: The Isolation of Estrogenic Diols from the Urine of Pregnant Mares, J. Biol. Chem. **122:** 303 (Jan.) 1938.

11. (*a*) Bachmann, W. E.; Cole, Wayne, and Wilds, A. L.: The Total Synthesis of the Sex Hormone Equilenin, J. Am. Chem. Soc. **61:** 974 (April) 1939; **62:** 824 (April) 1940. (*b*) Marker, R. E.: Reduction of Naphtholic Steroids to Phenolic Steroids: Equilenin, ibid. **60:** 1897 (Aug.) 1938.

12. Cook, J. W.; Dodds, E. C., and Hewett, C. L.: A Synthetic Oestrus-Exciting Compound, Nature, London **131:** 56 (Jan. 14) 1933. Campbell, N. R.; Dodds, E. C.; Lawson, W., and Noble, R. L.: Biological Effects of the Synthetic Oestrogen Hexoestrol 4: 4′-Dihydroxy-γ: ξ-Diphenyl-n-Hexane, Lancet **2:** 312 (Aug. 5) 1939. Dodds, E. C.; Goldberg, L.; Lawson, W., and Robinson, R.: Synthetic Oestrogenic Compounds Related to Stilbene and Diphenylethane, Proc. Roy. Soc., London, s. B, **127:** 140 (May 18) 1939; Oestrogenic Activity of Certain Synthetic Compounds, Nature, London **141:** 247 (Feb. 5) 1938. Dodds, E. C.; Lawson, W., and Noble, R. L.: Biological Effects of the Synthetic Oestrogenic Substance 4: 4′-dihydroxy-α: β-Diethylstilbene, Lancet **1:** 1389 (June 18) 1938. Robson, J. M., and Schönberg, A.: Oestrous Reactions, Including Mating, Produced by Triphenyl Ethylene, Nature, London **140:** 196 (July 31) 1937.

13. (*a*) Girard, André, and Sandulesco, G.: Sur une nouvelle série de réactifs du groupe carbonyle, leur utilisation à l'extraction des substances cetoniques et la caracterisation microchimique des aldéhydes et cetones, Helvet. chim. acta **19:** 1095, 1936. (*b*) Wintersteiner, Oskar: Estrogenic Diols from the Urine of Pregnant Mares, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1937, vol. 5, p. 25.

14. Miescher, K., and Scholz, C.: Ueber Ester der Follikelhormonreihe, Helvet. chim. acta **20:** 263, 1937; Ueber neue Verbindungen der Follikelhormonreihe, ibid. **20:** 1237, 1937.

15. (*a*) Kober, S.: Eine kolorimetrische Bestimmung des Brunsthormons (Menformon), Biochem. Ztschr. **239:** 209, 1931. (*b*) Cohen, S. L., and Marrian, G. F.: The Application of the Kober Test to the Quantitative Estimation of Oestrone and Oestriol in Human Pregnancy Urine, Biochem. J. **28:** 1603, 1934. (*c*) Bachman, Carl: Photometric Determination of Estrogens: A Modified Kober Reaction for Determining the Total Estrogens in a Mixture of Estrogenic Steroids, J. Biol. Chem. **131:** 455 (Dec.) 1939; A New Color Reaction for Estriol, ibid. **131:** 463 (Dec.) 1939.

16. (*a*) Butenandt, Adolf; Weidlich, H. A., and Thompson, H.: Neue Beiträge zur Konstitution des Follikel-hormons, Ber. d. deutsch. chem. Gesellsch. **66:** 601, 1933. (*b*) Haworth, R. D., and Sheldrick, George: Synthesis of Alkylphenanthrenes. 7-Hydroxy1: 2-Dimethylphenanthrene, J. Chem. Soc., London, 1934, pt. 1, p. 864. (*c*) Cohen, A.; Cook, J. W., and Hewett, C. L.: The Synthesis of Compounds Related to the Sterols, Bile Acids, and Oestrus-Producing Hormones. Experimental Evidence of the Complete Structure of Oestrin, Equilin and Equilenin, ibid. 1935, pt. 1, p. 445.

17. (*a*) Allen, Edgar: The Physiology of Estrogenic Principles, J. A. M. A. **104:** 1498 (April 27) 1935. (*b*) An excellent and extensive discussion of the physiology of the estrogens was given in Allen, Edgar; Danforth, C. H., and Doisy, E. A.: Sex and Internal Secretions, ed. 2, Baltimore, Williams & Wilkins Company, 1939.

18. Allen, Edgar; Francis, B. F.; Robertson, L. L.; Colgate, C. E.; Johnston, C. G.; Doisy, E. A.; Kountz, W. B., and Gibson, H. V.: The Hormone of the Ovarian Follicle; Its Localization and Action in Test Animals and Additional Points Bearing upon the Internal Secretions of the Ovary, Am. J. Anat. **34:** 133 (Sept.) 1924.

cells gave large cells with small nuclei or cornified cells typical of a response to estrogenic stimulation. This reaction has been used since 1923 in many assays of the estrogens. Without doubt the present advanced knowledge of the distribution and chemistry of the estrogens is due in large part to Edgar Allen's recognition of this reaction.

The work on vaginal smears has been extended to other species, but perhaps the most interesting development is the correlation by Papanicolaou [19a] of the change in the vaginal smear with other phenomena of the sex cycle of women. Subsequently, Papanicolaou and others [19b, c] have used the change in the smear as a guide to estrogenic therapy.

Estrogenic therapy for gonorrheal vaginitis [20] of prepuberal girls is based on the growth and thickening of the vaginal epithelium. Accompanying this growth, there is deposition of glycogen, with formation of a more acidic secretion. Biopsy specimens have shown the enormous growth that can be produced by proper medication with estrogens.

In the study of vaginal growth in animals the effects of colchicine [21] have yielded interesting results. Although this drug does not stimulate mitosis, it arrests dividing cells in the metaphase, thereby causing accumulation of many mitotic figures. This has permitted observation of the marked increase of mitosis due to the injection of estrogens.

Uterine and Tubal Reactions.—The injection of estrogens produces cell division in both the epithelium and the muscular layers of the uterus. With the use of colchicine it has been possible to demonstrate clearly the increased cell division occurring in both the tubes and the uterus after injection of estrogens. In addition to the growth there is definite development of the uterine glands, with an increase in the amount of secretion in the lumens of the uterus and tubes. Markee's [22] experiments in which a piece of endometrium was transplanted to the anterior chamber of the eye furnished an opportunity to observe in the living animal the effects of injections of estrogens, ovariectomy and related procedures.

Early work indicated that the administration of liquor folliculi to ovariectomized rats produced changes in the uteri indistinguishable from those in the uteri of rats in normal estrus.[23] Since this has been confirmed, using pure crystalline estrogens, there can be no doubt that estrogens are responsible for the growth and hyperplasia observed during the estrous cycle of the rat and mouse. Moreover, Allen and others have shown that estrogens produce growth and hyperplasia in ovariectomized monkeys and that after cessation of injections bleeding occurs. This seems to be identical with the anovulatory menstruation of the monkey (Corner).

The increase in weight of the uterus following administration of estrogen was used for assay prior to the introduction of the vaginal smear. Recently, several investigators [24] have returned to the stimulation of uterine growth as a method of assay. However, it should be emphasized that with this procedure the animal can be used for only one assay.

Astwood and collaborators [25] have contributed an interesting analysis of the changes that occur in the uterus in response to the injection of estrogen. Six hours after the injection the uterine weight has increased appreciably, but the addition is due to water. Twenty-four hours later the composition of the uterus has been restored to normal, although the weight is greater than at the six hour interval.

In addition to the effects on the circulatory system and on uterine and tubal growth, estrogens have a pronounced effect in increasing uterine motility.[26]

The discrepancy between the observations of different investigators as to the effect of estrogens on pregnancy seems to have been satisfactorily explained by the experiments which showed that administration of estrogen shortly after coitus causes locking of the tubes, in rabbits and mice.[27] The fertilized ova remain in the tubes and do not continue their development.

Mammary Reaction.—Growth of both the nipple and the mammary gland is stimulated by estrogens.[28] Sand has used the development of the nipples of males as an indication of the survival of transplanted ovaries.

In several species the injection of estrogen stimulates growth of the ducts, but in the guinea pig both ducts and alveoli respond with increased development. In strains of female mice which usually acquire mammary cancer the malignant growth is prevented by early ovariectomy. Moreover, Lacassagne has shown that the males of strains in which the females are susceptible to mammary cancer also show cancer in that gland if subjected to a course of estrogen injections.[29]

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Reactions of the Anterior Lobe of the Pituitary.—Castration is followed by cytologic changes in the anterior lobe of the pituitary, and the cytologic changes can be reversed by administration of estrogens. In addition to the cytologic change following castration, the anterior lobe contains an increased quantity of gonadotropin.[30]

In young rats the administration of a large quantity of estrogen is followed by luteinization of the ovaries. According to one view, this is due to release of a luteinizing product of the anterior lobe of the pituitary. If the injection is continued over a longer period, the ovaries diminish in size, although the uterus and vagina show the effect of estrogenic stimulation. However, experiments have shown that the ovaries have suffered no permanent damage, since female rats which had been given daily injections for a month produced normal litters. Since this point has considerable importance in the treatment of gonorrheal vaginitis in girls, Allen and Diddle have studied the effect of prolonged treatment in monkeys. No permanent damage could be detected.[31]

In addition to their effect in altering the gonadotropic output of the anterior lobe, injection of estrogen exerts a suppressing effect on the output of the lactogenic factor and indirectly on the secretion of milk.[32]

Effect on Calcium.—Although the effect on the serum calcium of birds has been a controversial point, it seems that massive quantities of estrogens do produce a striking increase. In the mouse, Gardner and Pfeiffer [33] have shown marked disturbances in calcium metabolism, in which the pelves show resorption and the long bones show an increase in density due to the replacement of marrow by bone spicules.

Effect on Fowls.—In some varieties of birds feathering is influenced by the sex hormones. In addition to the production of female feathering estrogens produce hypercalcification of bones and an increase in serum calcium and blood lipids. Although the increase in lipids due to the injection of estrogens is very marked, the values are not so high as those observed during the laying season.[34]

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BIOASSAY OF ESTROGENS

Although an additional standard for the estrogen benzoates was provided by the Permanent Commission on Biological Standardization at the last meeting of the League of Nations (1935), it was the opinion of the participants that "as rapidly and as far as possible, the production of preparations of the oestrus-producing hormones should be limited to pure preparations of the different forms of the hormone and its chemically defined derivatives or of mixtures thereof, so that the activity may be indicated in exact weights, and indications in biological units may be abandoned." [35]

In my opinion it is not feasible to assay against a standard any estrogen other than the estrogen of which the standard is composed. Only two standards have been furnished: estrone and α-estradiol monobenzoate. The members of the Commission realized that only preparations of estrone could be assayed satisfactorily against the estrone standard and only esters against the α-estradiol monobenzoate. To illustrate the discrepancies of assay when another estrogen is assayed against the estrone standard, estriol has been compared with estrone, mice being used for the assay. If each substance is given in a single injection of oil, the estrone is two hundred and sixty-six times as potent as estriol. If each is given in aqueous solution in four equal portions at intervals of twelve hours, the estrone is four times as potent as estriol. Depending on the solvent and on the division of the dose, estrone may be four or two hundred and sixty-six times as potent as estriol.

A similar situation exists with respect to the relation existing between estrone and α-estradiol. When each is given in aqueous solution in three portions during a nine hour period, the α-estradiol is ten times as active as estrone if rats are used for the assay but only twice as potent if mice are used.

In view of the past experience that each investigator has seemed unwilling to follow the assay procedure that a previous investigator has used, it appears that it would be wise to agree that since bioassay has served its purpose in guiding chemists to the preparation of pure estrogens, it should now be discarded, the products for therapeutic use labeled in metric units and their evaluation effected by the response of patients.

Metabolism of Estrogens.—A number of investigations have shown that the natural estrogens on administration to rats and mice are much less active when given orally than when given parenterally. It seems likely that the low potency following oral administration is not due to failure of absorption but rather to the fact that through the portal circulation the absorbed substance is offered first to the liver. Estrogens are rapidly destroyed by liver brei. Moreover, it has been shown that the heart-lung-liver preparation rapidly destroys estrogen, whereas the same system without the liver has little or no destructive action. A recent report gives interesting data on the effects of various tissue slices and of brei on estradiol, estrone and estriol.[36]

After parenteral administration, only a small proportion of estrogen can be recovered from tissues or excreta.[37] Even measures to hydrolyze possible conjugated and less active forms did not appreciably increase the recovery. Two reactions which might explain the loss merit consideration: (1) oxidation and (2) reduction. The phenolic portion of the molecule (ring A) is a point of weakness at which oxidation can take place. In the urine of nonpregnant women Marker found two inactive reduced forms, estranediol A and estranediol B. Since these compounds have not been found in pregnancy urine, Marker believes that the metabolism of estrogens in the pregnant and the nonpregnant woman follows different pathways.

35. Report of the Second Conference on the Standardization of Sex Hormones. League of Nations Quart. Bull. Health Organ. **4:** 618, 1935.

36. (*a*) Zondek, Bernhard: Ueber das Schicksal des Follikelhormons (Follikulin) im Organismus, Skandinav. Arch. f. Physiol. **70:** 133, 1934. (*b*) Israel, S. L.; Meranze, D. R., and Johnston, C. G.: The Inactivation of Estrogen by the Liver. Observations on the Fate of Estrogen in Heart-Lung and Heart-Lung-Liver Perfusion Systems, Am. J. M. Sc. **194:** 835 (Dec.) 1937. (*c*) Heller, C. G.: Metabolism of the Estrogens, Endocrinology **26:** 619 (April) 1940.

37. Zondek [36a] Westerfeld, W. W.: The Inactivation of Oestrone, Biochem. J. **34:** 51 (Jan.) 1940. Marker, R. E.; Rohrmann, Ewald; Lawson, E. J., and Wittle, E. L.: The Isolation of Oestranediols from Human Non-Pregnancy Urine, J. Am. Chem. Soc. **60:** 1901 (Aug.) 1938.

Several reports indicate that progesterone influences the metabolism of estrogen. A larger proportion of the injected estrogen is recovered when the organism has been treated with progesterone. Under these conditions a larger proportion of estrone or estradiol is converted to estriol. In the hysterectomized rabbit this change does not occur, thereby indicating that the uterus plays a part in the metabolism.[38]

ESTROGENIC THERAPY

The earlier attempts at estrogenic therapy with aqueous solutions did not yield results that were entirely satisfactory. This was due in part to the limitation of the solubility of estrogens in aqueous solution and to rapid absorption and excretion. This situation was met by using neutral triglycerides, in which the estrogens are much more soluble and from which absorption occurs more slowly. At the present time some physicians are experimenting with pellet therapy, in which a compressed tablet of estrogen is introduced directly under the skin. In spite of certain obvious objections, this form of administration does insure slow continuous absorption of the estrogen over a long period.[39]

From experiments on animals it seems that vaginal suppositories should be more effective than any other form of administration if it is desired merely to produce growth of the vaginal epithelium. Possibly this form of therapy is ideal for gonorrheal vaginitis in that responses other than vaginal may be restricted.[40]

Although oral therapy may be more popular with patients, it seems that physicians have generally used preparations for parenteral use. No doubt, this was due in part to the prevailing evidence that in animals the natural estrogens were twenty or more times as active parenterally as enterally and in part to the desire on the part of the physician to secure more satisfactory control of therapy. Perhaps the recent experimentation with synthetic estrogens, ethinyl estradiol and stilbestrol, which are more active orally in animals will lead to an increased use of oral preparations when it has been satisfactorily established that such therapy is without danger.

With every woman of 40 years a prospective patient and actually a high percentage sooner or later being treated with estrogens, an experiment of tremendous magnitude is in progress. The acute undesirable reactions from ethinyl estradiol and stilbestrol which have been reported by some physicians have served as a definite warning that caution should be exercised.[41] Furthermore, there seems during the last five years to be a definite trend toward massive dosage with both natural and synthetic estrogens. Perhaps this will eventually prove to be satisfactory, but in the meantime it does not seem wise to be too incautious. Within another five or ten years any subacute damage which may have occurred will begin to make its appearance.

The increased incidence of malignant change following administration of estrogens to cancer-susceptible strains of animals serves as a definite warning. While it is true that the dose per kilogram of body weight is much higher than the amounts commonly used therapeutically in the human patient and that the most pronounced carcinogenic reactions are obtained in susceptible animals, still it seems unwise to ignore the possibility of accelerating or starting the growth of cancer in susceptible persons. Certainly, the treatment of patients having cancer or of patients from families with a history of cancer should be undertaken with a full recognition of the possibility of untoward results.

38. Pincus, Gregory, and Zahl, P. A.: The Biogenesis of Primary Sex Hormones: The Fate of Estrins Injected into the Rabbit, J. Gen. Physiol. **20:** 879 (July) 1937. Smith, G. V., and Smith, O. W.: Observations Concerning the Metabolism of Estrogens in Women, Am. J. Obst. & Gynec. **36:** 769 (Nov.) 1938. Smith, G. V.; Smith, O. W., and Pincus, Gregory: Total Urinary Estrogen, Estrone and Estriol During a Menstrual Cycle and a Pregnancy, Am. J. Physiol. **121:** 98 (Jan.) 1938. Pincus, Gregory, and Graubard, Mark: Estrogen Metabolism in Cancerous and Non-Cancerous Women, Endocrinology **26:** 427 (March) 1940.

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Council on Pharmacy and Chemistry

REPORT OF THE COUNCIL

THE COUNCIL HAS AUTHORIZED PUBLICATION OF THE FOLLOWING STATEMENT.

THE COUNCIL ACCEPTS FOR INCLUSION IN N. N. R. SOME PRODUCTS OF ENDO PRODUCTS, INC.

Until recently no product of Endo Products, Inc., has been accepted by the Council on Pharmacy and Chemistry because of conflicts with the rules of the Council. On Jan. 12, 1938, the firm stated that it wished to cooperate with the Council. The firm has demonstrated its willingness to remove certain causes of conflict and has sent the Council a number of revisions of its catalogues. After considerable correspondence and negotiations, the Council voted to remove application of rule 11 from Endo Products, Inc. This action became effective June 5, 1940.

NEW AND NONOFFICIAL REMEDIES

THE FOLLOWING ADDITIONAL ARTICLES HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO NEW AND NONOFFICIAL REMEDIES. A COPY OF THE RULES ON WHICH THE COUNCIL BASES ITS ACTION WILL BE SENT ON APPLICATION.

OFFICE OF THE SECRETARY.

POLLEN ALLERGEN SOLUTIONS-SQUIBB (See New and Nonofficial Remedies, 1940, p. 37).

The following additional product, marketed in 5 cc. vials and having a potency of 10,000 protein nitrogen units per cubic centimeter, has been accepted:

Ragweed and Cocklebur Combined Pollen Extract-Squibb: (giant ragweed, dwarf ragweed, and cocklebur pollen extracts in equal proportions).

RACEPHEDRINE (See New and Nonofficial Remedies, 1940, p. 242).

The following product has been accepted:

Racephedrine Hydrochloride-Upjohn.—A brand of racephedrine hydrochloride-N. N. R.

Manufactured by The Upjohn Company, Kalamazoo, Michigan. No U. S. patent or trademark.

Racephedrine Hydrochloride 1% in Modified Ringer's Solution: Contains in each 100 cc. racephedrine hydrochloride-N. N. R., 1 Gm., chlorobutanol, 0.5 Gm., sodium chloride, 0.85 Gm., potassium chloride, 0.03 Gm., calcium chloride, 0.025 Gm. and magnesium chloride, 0.01 Gm. dissolved in distilled water.

Capsules Racephedrine Hydrochloride ¾ Grain.

SULFANILAMIDE (See New and Nonofficial Remedies, 1940, p. 489).

The following dosage form has been accepted:

Tablets Sulfanilamide, 1 grain-The Upjohn Company.

Prepared by The Upjohn Company, Kalamazoo, Mich. No U. S. patent or trademark.

Council on Foods and Nutrition

THE COUNCIL HAS AUTHORIZED PUBLICATION OF THE FOLLOWING REPORT. FRANKLIN C. BING, Secretary.

DESSERTS IN THE DIETS OF ADULTS AND YOUNG CHILDREN

It is the custom to conclude most meals, except breakfast, with some sweet, appetizing food which is more than ordinarily attractive in appearance as well as flavor. Such foods are known in the United States as desserts. Although some products in this class are of comparatively recent origin, the practice of ending a meal with a small portion of a sweet, attractive food appears to be as old as recorded history.

PHYSIOLOGIC SIGNIFICANCE

From the physiologic point of view the custom of ending the meal with a dessert probably serves two purposes, that of completely satisfying the appetite and that of providing a final psychic stimulus to the secretion of gastric juice. Those desserts with a high content of sugar or fat or both have a high satiety value. The presence of the sensation of appetite (and of the appetite secretion) is evidence of the physiologic fitness of the gastrointestinal tract to handle the food eaten, although normal digestion will proceed in the complete absence of appetite juice, which is secreted as a result of the sight, smell or taste of appetizing foods. Thus the serving of an attractive, palatable dessert may be considered a useful, though not indispensable, factor in the proper conditioning of the digestive tract for the performance of its normal function.

THE NUTRITIONAL SIGNIFICANCE OF DESSERTS IN THE DIET OF THE ADULT

Desserts vary widely in nutritional value, according to the ingredients of which they are composed. A dessert should be selected not alone for its appetite appeal but for its food value as well. Due consideration should be given to the contribution of the dessert to the composition of the diet as a whole.

Those foods now commonly used as desserts include fruit, pastry of all kinds, such as pies, cakes and other baked goods, pudding of all types, and the universally popular ice creams and other frozen desserts. The differences which may be found in the composition of average portions of representative desserts selected from each of the foregoing categories are illustrated in table 1. In general the table shows that those desserts which are richest in calories are proportionally poorest in other dietary essentials. This is explained by the fact that the higher calory desserts such as cake and various other types of pastry are composed largely of refined sugar, fat (butter or, perhaps more often, some other suitably prepared animal or vegetable fat) and highly milled wheat flour. These ingredients, except butter, are notably deficient in dietary essentials other than calories. The table also shows that the nutritional values, other than calories, of desserts such as custard or apple pie are less than those of baked custard or baked apple alone. Thus the pastry may be said to "dilute" the essential dietary value of the fruit or custard. If a method adopted by the Council for the rating of foods as sources of the various dietary essentials is applied [1] it is found that only the fresh fruits or those desserts in which milk or dairy products are the predominating ingredients can be rated as nutritionally significant sources of any of the dietary essentials other than calories. This method takes into account the caloric value of the food as well as the total daily requirement and the quantity of any given dietary essential which is supplied by a portion which can be conveniently eaten in one day.

The adult whose regular occupation demands a large expenditure of physical energy, or the physically active adolescent, usually may indulge moderately in cakes, other forms of pastry or other desserts which are rich in calories. Indeed, these desserts are sometimes a convenient and palatable source of the relatively large amounts of food energy the active person requires. It is essential, however, that the amount of calory-rich dessert which is eaten does not reduce the intake of other essential food substances. Also desserts containing large proportions of sugar probably should be avoided even by physically active persons if they appear to be unusually susceptible to dental caries.

Persons who lead less active lives, particularly sedentary persons of small stature, require fewer calories, and the amount of high calory dessert eaten must be carefully restricted if the diet is to be adequate in proteins, minerals and vitamins and at the same time is to remain within the limits of the calory requirement. When planning adequate diets for the sedentary adult and the young child it is usually much simpler to attain success if high calory desserts are completely eliminated from the menu. When included, even in modest quantities, it is difficult to plan a diet that is adequate in dietary essentials other than calories except for persons who require more than 2,500 calories daily.

TABLE 1.—*Approximate Composition of Some Representative Desserts*

Name of Product	Weight, Gm.	Approximate Measure	Calories	Protein, Gm.	Calcium, Gm.	Phosphorus, Gm.	Iron, Mg.	Vitamins (I. U.) A	Vitamins (I. U.) B_1	Vitamins (I. U.) C
Cake, plain, 2-layer, vanilla icing	100	1 pc. (1/12 cake)	362	3.9	0.020	0.048	0.46	83	8	
Cake, chocolate, 2-layer, vanilla icing	100	1 pc. (1/12 cake)	388	4.3	0.049	0.088	0.62	248	11	
Ice cream, vanilla	...	1/8 qt.	245	3.7	0.124	0.103	0.23	426	9	
Ice cream, chocolate	...	1/8 qt.	285	4.1	0.130	0.142	0.40	426	9	
Tapioca pudding	...	1/2 cup	148	4.9	0.105	0.112	0.72	261	19	
Custard, baked	...	1/2 cup	202	8.9	0.165	0.195	1.33	492	33	
Pie, custard	...	1/6 medium pie	263	6.3	0.107	0.129	0.81	261	19	
Cream puff (éclair) custard filling	80	1 average	194	4.0	0.059	0.080	0.62	198	13	
Gelatin, lemon	...	1/2 cup	82	1.2	0.001	0.001	0.04	...	+	?
Apple, baked	115	1 large, 2T brown sugar	181	0.5	0.032	0.020	1.32	100	12	12-32
Pie, apple	...	1/6 medium pie	406	2.6	0.011	0.038	0.58	108	<11	?
Banana, fresh	100	1 small	99	1.2	0.008	0.028	0.65	400	18	20-300
Grapes, American	100	1 bunch, 22-24 average	78	1.4	0.019	0.035	0.73	15-90	10	20-144
Strawberries, fresh	100	10 large	41	0.8	0.034	0.028	0.68	100	<8	1,000
Watermelon	100	1/2 cup cubes or balls	31	0.5	0.007	0.013	0.23	125	18	300

Values for all products derived from Anna de Planter Bowes and C. F. Church; Food Values of Portions Commonly Used, third edition, available from Anna de Planter Bowes, Philadelphia Child Health Society, Philadelphia, 1940.

TABLE 2.—*Proportions of Ingredients of Some Simple Home-Prepared or Institution-Prepared Desserts*

	Milk, %	Fruit or Fruit Juice, %	Milk and Fruit, %	Eggs, %	Added Carbohydrates, %
Cornstarch pudding (blanc mange)	91.2	....	....	....	8.7
Baked custard	79.1	....	....	15.3	5.6
Rice pudding	81.8	8.1	89.9	....	10.1
Cream tapioca pudding	74.1	....	....	14.3	11.6
Prune tapioca pudding	52.9	27.7	80.6	10.2	8.9
Orange tapioca	25.2	27.8	53.0	....	20.0
Fruit gelatin dessert	....	77.2	....	....	....

Data for all products except fruit gelatin dessert are derived from recipes given by Mary E. Sweeney and Dorothy C. Buck: How to Feed Young Children in the Home, Merrill Palmer School, Detroit. Data for fruit gelatin dessert are derived from the recipes given by Mary E. Sweeney and Dorothy C. Buck: How to Feed Children in Nursery Schools, Merrill Palmer School, Detroit.

1. Accepted Foods and Their Nutritional Significance, American Medical Association, Chicago, 1939.

Reducing or other calory-restricted diets frequently are limited to 1,500 calories or less. The milk, vegetables and other so-called protective foods which are the chief source of essential vitamins and minerals in the customary American diet themselves provide in the neighborhood of 1,000 to 1,500 calories when used in the amounts recommended by most experts in nutrition. Thus, in reducing diets the use of high calory desserts must be avoided. If used, these products inevitably will crowd out other and more essential foods or will result in a calory intake in excess of the requirement. Thus there results either more or less serious malnutrition, or the diet fails to accomplish its purpose of weight reduction. Desserts suitable for use in reducing or other calory-restricted diets are those which are themselves comparatively low in calories and which in addition provide nutritionally significant amounts of one or more dietary essentials other than calories. The data provided in table 1 show that fruits served without sugar or cream are preeminent among the desserts which meet these requirements.

DESSERTS FOR YOUNG CHILDREN

To provide adequate amounts of essential food constituents the diets of normal, healthy children usually should contain the following "protective" foods in approximately the quantities listed:

Milk, three or four cups daily.

Vegetables, two servings daily; if possible two besides potatoes. Green or yellow vegetables at least three or four times a week and preferably daily.

Fruit, one or two servings every day, with emphasis on citrus fruit or tomato juice. At least one of the fruits or vegetables should be served raw, particularly if citrus fruits or tomatoes are not readily available.

Three or more pats of butter or of oleomargarine which has been fortified with vitamin A. (Unfortified oleomargarine is undesirable in the diets of children because of its lack of vitamin A.)

Whole-grain cereal or whole-wheat bread or its nutritional equivalent in "restored" products, at least one and preferably two or more servings daily.

One or two servings of a protein-rich food other than milk, especially as the child grows older.

These foods alone will supply, in the portions suited to the young child, from approximately 1,200 to 1,800 calories. The total calory requirements of normal, active preschool children are of approximately the same order of magnitude. Thus it is apparent that, if the necessary nutritional values are to be provided, the diets of young children should not be "diluted" with desserts or other foods which serve only as a source of calories. If a dessert is to be included in the young child's diet it should carry its full share of the various dietary essentials.

In the distribution of the essential foods in the simple menus appropriate for the preschool child the citrus fruit or tomato juice, which serves as the main source of vitamin C, is customarily given as the breakfast fruit or as a part of a regularly scheduled midmorning feeding. The second portion of fruit, if two portions are given, may serve as the dessert for either the noon or the evening meal. The fresh or cooked fruit is best served alone and undiluted. Occasionally, for variety, the slightly sweetened undiluted fruit juice may be stiffened with gelatin and served with a suitable topping, or the fruit may be combined with other appropriate ingredients in the preparation of a simple pudding.

Milk also lends itself to the preparation of a wide variety of desserts, in which it may be used alone or combined with other essential foods such as eggs, whole grain cereal, and fruit or fruit juices. Such use of milk not only provides a satisfying and appetizing finish to the meal but affords an opportunity to vary the form in which this essential food is fed. This is frequently an important factor in inducing children to take the amounts of milk which are considered desirable.

REQUIREMENTS FOR ACCEPTED DESSERT PRODUCTS FOR YOUNG CHILDREN

There now are being marketed a number of prepared dessert products intended for feeding to invalids or to young children. No federal standards for the composition of these products as a class have been established. The Council, in considering such commercial products, has found it necessary to arrive at some nutritional standards for acceptable products in this group.

Acceptable commercial dessert products intended for use in the feeding of children or invalids should not be nutritionally inferior to home-made desserts which are considered suitable for this purpose. The average proportions by weight of milk, fruit or fruit juice and other ingredients used in the home or institutional preparation of several simple desserts, which are suitable for young children, are listed in table 2. This table shows that the majority of these products contain at least 75 per cent of milk or fruit or of a combination of milk and fruit (or undiluted fruit juice) and that none contain less than 50 per cent of these ingredients. These proportions are therefore considered representative of good practice in the preparation of children's desserts.

On the basis of these facts and of the considerations discussed in the foregoing paragraphs, the Council has reached the decision: To be acceptable to the Council, commercial dessert products represented for use in the feeding of young children must contain milk or fruit or a combination of these two ingredients in amounts which constitute at least 50 per cent of the total weight of the product. Prepared desserts which contain less than 50 per cent by weight of milk or fruit or a combination of milk and fruit are not considered eligible for acceptance or for description in the book Accepted Foods and Their Nutritional Significance.

ACCEPTED FOODS

THE FOLLOWING ADDITIONAL FOODS HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON FOODS OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO ACCEPTED FOODS.

FRANKLIN C. BING, Secretary.

PREPARATIONS USED IN THE FEEDING OF INFANTS (*See* Accepted Foods, p. 156).

H. J. Heinz Company, Pittsburgh.

HEINZ BRAND APPLE, FIG AND DATE DESSERT, a canned cooked mixture of apples, figs, dates, sugar and lemon juice.

Analysis (submitted by manufacturer).—Moisture 74%, total solids 26%, ash 0.6%, fat (ether extract) 0.2%, protein (N × 6.25) 0.6%, crude fiber 1.0%, carbohydrates other than crude fiber (by difference) 23.6%, sucrose (Munson and Walker method) 21.3%, calcium (Ca) 0.039%, phosphorus (P) 0.019%, iron (Fe) 0.0027%, copper (Cu) 0.00012%.

According to report of biologic assay (1939) this product contains 7 international units of vitamin A, 6 international units of vitamin B_1 and 17 Sherman-Bourquin units of riboflavin per hundred grams. Report of chemical titration (1939) shows that the product contains 50 international units of vitamin C per hundred grams.

Calories.—1 per gram; 28 per ounce.

HEINZ BRAND LAMB AND LIVER STEW WITH MILK AND CEREALS, a canned cooked mixture of milk, white potatoes, lamb, celery, lamb livers, cream, carrots, rice, onions, corn starch, chicken livers, and sodium chloride.

Analysis (submitted by manufacturer).—Moisture 84.7%, total solids 15.3%, ash 1.3%, fat (ether extract) 2.2%, protein (N × 6.25) 2.9%, crude fiber 0.7%, total carbohydrates other than crude fiber (by difference) 8.2%, sucrose (Munson and Walker method) 1.7%, calcium (Ca) 0.065%, phosphorus (P) 0.063%, iron (Fe) 0.0055%, copper (Cu) 0.00018%.

According to report of biologic assay (1939) this product contains 3,100 international units of vitamin A, 9 international units of vitamin B_1 and 73 Sherman-Bourquin units of riboflavin per hundred grams. Report of chemical assay (1939) shows that the product contains 64 international units of vitamin C per hundred grams.

Calories.—0.64 per gram; 18 per ounce.

HEINZ BRAND PINEAPPLE RICE PUDDING, a canned cooked mixture of crushed pineapple, milk, sugar, rice, eggs, cornstarch and sodium chloride.

Analysis (submitted by manufacturer).—Moisture 70.3%, total solids 29.7%, ash 0.7%, fat (ether extract) 0.6%, protein (N × 6.25) 0.3%, crude fiber 0.3%, carbohydrates other than crude fiber (by difference) 27.8%, sucrose (Munson and Walker method) 17.5%, calcium (Ca) 0.051%, phosphorus (P) 0.033%, iron (Fe) 0.0014%, copper (Cu) 0.00008%.

According to report of biologic assays (1939) this product contains 38 international units of vitamin A, 9 international units of vitamin B_1 and 28 Sherman-Bourquin units of riboflavin per hundred grams. Report of chemical titration (1939) shows that this product contains 16 international units of vitamin C per hundred grams.

Calories.—1.18 per gram; 34 per ounce.

HEINZ BRAND PRUNE PUDDING, a canned cooked mixture of milk, prune pulp, sugar, farina, eggs, cornstarch and sodium chloride.

Analysis (submitted by manufacturer).—Moisture 70%, total solids 30%, ash 1%, fat (ether extract) 1.2%, protein (N × 6.25) 2.4%, crude fiber 1.2%, carbohydrates other than crude fiber (by difference) 24.2%, sucrose (Munson and Walker method) 17.3%, calcium (Ca) 0.069%, phosphorus (P) 0.054%, iron (Fe) 0.0011%, copper (Cu) 0.00016%.

According to report of biologic assay (1939) this product contains 300 international units of vitamin A, 10 international units of vitamin B_1 and 70 Sherman-Bourquin units of vitamin G per hundred grams. Report of chemical titration (1939) shows that the product contains 64 international units of vitamin C per hundred grams.

Calories.—1.17 per gram; 33 per ounce.

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SATURDAY, FEBRUARY 8, 1941

HEALTH AND PHYSICAL EDUCATION UNDER FEDERAL SUPERVISION

During the closing days of the last Congress a measure was submitted, under the sponsorship of the American Association for Health, Physical Education and Recreation, proposing federal appropriations totaling eventually $200,000,000 a year "to promote national preparedness and the national welfare" by assisting the several states and territories in making adequate provisions for "health education, physical education and recreation in schools and school camps." The framework of this bill followed the customary pattern of federal subsidy legislation. State plans were to be submitted by state educational authorities for approval by the federal official to be charged with the administration of the bill, the United States Commissioner of Education. Throughout the proposal references were made to the important problem of health education of persons between the ages of 5 years and 20 years in schools and in school camps. A state school plan was required to provide, among other things, for a continuous school health service, exclusive of medical and dental treatment, to determine at least annually the health status of each pupil, for special health instruction for handicapped children, for health supervision to insure safe and sanitary school conditions "and processes for healthful living," and for instruction in nutrition, dental hygiene, first aid, effects of narcotic drugs and alcohol, and physical and mental hygiene. Similarly, in plans for school camps instruction in matters relating to health was to play an important role. Scant suggestion was to be found in the bill that the services of those most competent to deal with health problems, whether in schools, in school camps or elsewhere, were to be utilized in making effective its stated objectives. This measure did not receive congressional consideration and consequently died when the Congress automatically expired. Now a similar bill, in a modified form, is before the new Congress, H. R. 1074, introduced by Representative Schwert of New York. In its structure it follows its prototype, but specific references to problems of health education such as those mentioned have been omitted. There has been added, however, a most unusual provision to the general effect that the scope of the activities to be carried on under the bill may be extended in a particular state apparently without any limit whatever if the legislature of that state decrees. Thus any state legislature could add the medical features which have been eliminated from the federal measure. The proposal suggests a most ambitious program, which is offered for prompt action as a part of national preparedness. No doubt hearings can be held to determine the need for the measure and the scope of activities it is planned to embrace.

This legislation is symptomatic of a widespread movement in physical education. The College Physical Education Association [1] has adopted a report of a special committee in which the importance of physical education to the defense of democracy is emphasized. This report points out that physical education includes programs of health education and physical education. It presents a series of recommendations for national organization and legislation, for defining the responsibilities of the association, for outlining local programs, for activity programs, for military training and drill, for health instruction, for health service and for professional training. In brief, the College Physical Education Association holds that it should study every piece of proposed federal legislation in this field and support "desirable federal legislation aimed at the improvement of the health of the people and the development of physical education, health education and recreation in the several states." The services of its members are offered to the federal defense authorities and the War and Navy departments and to the National Defense Council, as well as to the United States Public Health Service and to the United States Civil Service Commission for use in the development of national, state or local programs in health education or recreation. Cooperation is tendered also to other physical, health education and recreational associations "and others." The proposal recommends "that, in the main, no radical or sharp departures in the content of local programs be advised," but that efforts be made "to intensify and improve the activity programs" now under way. Extensive recommendations are made for activity programs, health instruction and health service, endorsing both military training and physical education but holding that neither should be regarded as a substitute for the other.

Under health service, thorough physical examinations and immunization programs are recommended, and it is suggested that all physical education activities be conducted in accordance with the results of medical examinations. The report recommends "that the col-

1. Report of the Committee on the Contribution of College Physical Education to National Preparedness, New York, College Physical Education Association, Dec. 30, 1940.

lege assume some responsibility for making appropriate medical or surgical service available to all students in need thereof." It urges that all opportunities be seized for the improvement of professional training.

The American Legion has published a national program of preparedness and defense through physical education, health education and recreation in schools and communities.[2] This is a twenty-nine page letter to its national and state offices outlining the program, of which the salient feature is that the legion stands ready to cooperate with existing agencies in the improvement and extension of existing programs in health education, physical education and recreation.

Physicians look with sympathetic interest on the desire to improve the health education and physical status of the American people and on contributions to wholesome recreations. They approve such proposals as the coordination of physical activities with medical observations and the promotion of programs of preventive medicine and dentistry, as well as the wider dissemination of information about healthful living. Physicians approve especially plans which wisely utilize, extend and improve the good work that is now being done. They oppose the expenditure of large sums of money on experimental programs or activities which call on unqualified persons to perform functions which belong in the medical sphere. The national defense will not be served merely by the injudicious increase of expenditures. The American people, as THE JOURNAL [3] has already pointed out, is not a nation of physical weaklings, even though it may not have achieved a maximum of good health and physical fitness.

THE OXFORD TUBERCULOSIS VACCINE

Among the basic medical researches interrupted by the present European war, none are of greater clinical interest than the Oxford University [1] studies of the vole acid-fast bacillus as a prophylactic vaccine against human or bovine tuberculosis. Although the experimental evidence thus far collected by Wells and Brooke is regarded by them as statistically inconclusive, their evidence is nevertheless sufficiently striking to warrant the hope that the vole vaccine may in time prove to be of clinical value.

Three years ago Wells,[2] of the Sir William Dunn School of Pathology, Oxford University, described a fatal tuberculosis-like disease of the wild voles of the British Isles, from which he isolated a hitherto undescribed acid-fast bacillus. The vole bacillus grows readily on Dorset's egg medium and will reproduce fatal tuberculosis-like disease if injected subcutaneously into laboratory bred voles but is almost devoid of pathogenicity for rabbits or guinea pigs. Massive doses (e. g. 5 to 10 mg.) of the living bacillus injected subcutaneously into guinea pigs may occasionally produce progressive disease and death. A smaller inoculum (e. g. 1 mg.) usually produces only a local abscess with occasional ulceration, which invariably heals spontaneously.

In their initial test of the immunizing power of this bacillus, a group of 3 guinea pigs was inoculated in the left groin with caseous material from naturally infected wild voles. Each guinea pig developed a local caseous lesion, but there was no sign of a generalized infection. Nine months later, after complete healing of the local lesion, each guinea pig, together with normal control, was injected in the opposite groin with 10^{-6} mg. of a month old culture of bovine tubercle bacilli of low virulence. The animals were killed six months later. Necropsies of the control group revealed extensive generalized tuberculosis involving the lungs, liver, spleen and lymph glands. With one exception the vole-vaccinated guinea pigs showed no involvement of the internal organ, the only macroscopically demonstrable lesion being a small local caseous nodule in the right groin.

The test was then repeated on a larger scale, a freshly isolated highly virulent strain of human tubercle bacilli being employed as the test organism. One group of 5 guinea pigs was vaccinated with 1 mg. of the vole bacillus. A second group received one tenth of this dose. Three months later both groups, together with an equal number of unvaccinated controls, were inoculated with 10^{-5} mg. of highly virulent human tubercle bacilli. All nonvaccinated controls died within three months, necropsies showing extensive generalized tuberculosis. Both vaccinated groups were killed at this time. None of the animals receiving the larger dose of the vole vaccine had developed demonstrable internal lesions, necropsies showing only a small local abscess. Among the animals receiving a tenth dose of the vole vaccine, only 1 developed a partially generalized tuberculosis, all others showing only a regressive local lesion. A single 1 mg. dose of the vole vaccine apparently gave almost complete immunity, with a less effective prophylaxis from a tenth of this vaccine dose.

In order to form a basis of prediction for the probable clinical value of the vole vaccine, each of a group of 52 guinea pigs was given four weekly injections of 0.5 mg. doses of the vole bacillus. Each of a group of 30 control guinea pigs was given four 7.5 mg. doses of BCG. Previous studies had shown that this dose of BCG is the optimum immunizing dose for guinea pigs. Five months after the last injection, half of the sur-

2. The National Program of Preparedness and Defense Through Physical Education, Health Education and Recreation in School and Community. American Legion, Jan. 10, 1941.

3. Health of Young Men Under Selective Service, editorial, J. A. M. A. **116**: 54 (Jan. 4) 1941.

1. Wells, A. Q., and Brooke, W. S.: Brit. J. Exper. Path. **21**: 104 (April) 1940.

2. Wells, A. Q.: Lancet **1**: 1221 (May 22) 1937.

viving members of each group were injected with 10^{-6} mg. of highly virulent human tubercle bacilli, the second half receiving a test dose of 10^{-6} mg. of a highly virulent bovine tubercle bacilli. Control inoculations were made at the same time with an equal number of unvaccinated normal guinea pigs.

It was originally intended to keep all animals for eighteen months, or as long as they survived, to determine the survival time in each group. This was made impossible, however, because of the war. All animals were therefore killed at the end of eleven weeks. At necropsy all members of the unvaccinated group exhibited extensive generalized tuberculosis. Most of the animals given the vole vaccine exhibited no lesions or at most only a small regressive local abscess. Those given the BCG vaccine had all developed generalized tuberculosis, though usually less severe than in the control unvaccinated group. The degree of protection from the vole vaccine, therefore, is much greater than that induced with the optimum dose of BCG vaccine and therefore, in the opinion of the Oxford investigators, greater than any other tuberculosis vaccine thus far recorded.

Report of the interrupted Oxford experiments is published at this time in the hope that the encouraging preliminary data may be confirmed in nonbelligerent countries, with minimum loss of time in determining possible clinical or veterinary applications.

Current Comment

CIVILIAN PHYSICIANS TO ADVISE ARMY ON EPIDEMICS

Under Medical Preparedness in this issue of THE JOURNAL appears the announcement of the establishment of a board for the investigation of influenza and other epidemic diseases in the Army. The Surgeon General should be heartily commended for this significant and forward-looking action. During World War I, special boards composed of the most competent specialists available were asked by Surgeon General Gorgas to study epidemic conditions and to advise him as to methods of prevention and treatment. These boards rendered distinguished service. The Surgeon General has now anticipated the possibility of outbreaks of infectious diseases in the camps in which hundreds of thousands of young men are being trained and will have available a board of distinguished advisers who are ready for immediate assignment. Moreover, the order just approved by the general staff permits the utilization of any experts who may be required as consultants. It permits the establishment of investigative teams to be sent for temporary duty to military stations and gives opportunity for these distinguished civilian investigators to report directly to the Surgeon General, thus enabling the most prompt action possible. Unquestionably the creation of such a civilian advisory body will give to the fathers and mothers of this country a new confidence in the efficiency and watchfulness of the medical department of the United States Army.

"APPROVED" RADIOLOGISTS

The advances of medical science and medicine have made possible more elaborate methods of examination of patients, some of which may be carried out by the physician himself while others require the assistance of persons specially trained for the performance of these tasks. Those who may be called on for laboratory or radiologic service must be fully qualified for the responsibilities which they undertake. The House of Delegates of the American Medical Association in 1923 instructed the Council on Medical Education and Hospitals to prepare a list of approved clinical laboratories. Again in 1928 the House of Delegates instructed the Council to prepare a list of approved radiologic laboratories. In 1931 THE JOURNAL issued a Radiologic Number which included the names of qualified physicians specializing in radiology. Until 1936 this list, revised to date, was published annually and was generally accepted as constituting the most dependable source of information concerning those entitled to be regarded as specialists in this field. However, after the establishment of the American Board of Radiology, certification based on examination offered a more satisfactory basis for the recognition of qualified specialists than the listing on the basis of credentials, which was the only means available to the Council. The Council's list, therefore, was discontinued and the Council together with the medical profession generally has come to recognize the certificate of the American Board of Radiology as the most satisfactory means of identifying those who are really entitled to the confidence of the public. Since the listing of "Physicians Specializing in Radiology" was abandoned five years ago, a physician may not now justly claim to be "approved by the Council" or to announce in any manner that he enjoys such recognition.

INSURANCE AGAINST MULTIPLE BIRTHS

Josh Billings once said that there is one thing for which no man is ever quite prepared and that thing is twins. In his time the actuaries had not given serious consideration to the incidence of multiple births. Now they tell us that a plural birth occurs once in every eighty-eight pregnancies, which makes the odds reasonably certain except for the discount necessary because of the tendency toward inheritance of twinning. Nevertheless one insurance company, perhaps as a publicity stunt, now offers indemnity for multiple births, which it calls "plural birth insurance." For a premium of $15 a payment of $500 will be made, or for $25 an "indemnity" of $1,000 will be paid in the event that a plural birth occurs. The policy is not issued where there is record of twins on the male side. Since it is now known that the roentgen ray can reveal the presence of twins in the latter half of pregnancy, the company will not issue

a policy to cover births occurring within five months subsequent to the date of the application. So many things can happen to us nowadays that it is almost impossible to insure oneself against all of life's hazards. There is the possibility of fire, earthquake, tornado, accident, soot, burglary, loss of occupation, old age, golf, war and increased taxes. There is also the possibility that the necessary premiums to protect us against all the hazards which we may meet might eventually reach our total earning power. There are a number of risks that are more imminent than triplets and quadruplets. Moreover, as in the case of the Dionnes, there is the possibility that multiple births might eventually be a benefit. No doubt there are a number of prospective fathers right now who would be willing to venture a small premium if they could be given a reasonable guaranty of something happening in their lives like what the Dionne quintuplets have turned out to be.

BRINKLEY ON THE BRINK? III

Several months ago THE JOURNAL published an editorial dealing with various law suits pending against Dr. John R. Brinkley (Oct. 19, 1940, p. 1368). Subsequently (Nov. 9, 1940, p. 1655) THE JOURNAL published a story about the return of Dr. Brinkley to Del Rio, pointing out that Brinkley claimed he would have no financial interest in the reestablishment of a Brinkley Hospital at Del Rio. Under date of February 1 the Washington (D. C.) *Star* carried the following Associated Press release:

> San Antonio, Tex., Feb. 1.—Dr. John R. Brinkley, Del Rio gland surgeon, radio station operator and twice unsuccessful candidate for Governor of Kansas, has been adjudged bankrupt.
>
> The surgeon voluntarily petitioned for the judgment. A preliminary schedule, subject to amendment, listed debts scheduled but not admitted at $1,118,064.50, and assets at $316,500.

PHYSICIANS SHARE IN RELIEF FUNDS

The Wayne County (Mich.) Medical Society has completed a valuable and exhaustive study of the source and disposition of the tax dollar expended during 1938 in Wayne County for sickness and health. During the past year certain medical relief in Michigan was made a political issue. One group resorted to sensational charges that the medical profession was exploiting relief resources and that doctors were getting rich out of medical relief. As recorded in the *Detroit Medical News* for January 13, the report of the Section on Public Welfare Relations of the Medical Economic Commission of the Wayne County Medical Society shows that appropriations amounting to $16,288,265.70 were expended during 1938 by the different public authorities and private institutions in Wayne County for medical relief. Out of this sum, the physicians chosen by free choice, who have been the targets for most of the attacks, received $608,392.67, or 3.7 per cent of the total. When the proper deductions for services of private "physicians no longer authorized" are made, the percentage shrinks to 2.6. Hospitals received 75.4 per cent of the funds, which amounted to $12,268,044.48. The detailed report reveals information not generally available to the same extent for any other large city. It is a valuable contribution to medical economics.

WAR MEDICINE

In the section on Medical Preparedness in this issue of THE JOURNAL appears one of the first official reports prepared by the Division of Medical Sciences of the National Research Council for the guidance of medical officers of the Army and Navy medical departments. This outline of chemotherapy expresses the point of view of leaders in the field of pharmacology and therapeutics regarding the proper use of chemotherapy under military conditions. For the second issue of *War Medicine,* it is hoped to assemble a similar concentrated statement relative to the prevention and treatment of venereal diseases under military conditions. The first report has already been officially adopted by the United States Army Medical Department as Circular Letter No. 81. Regardless of whether or not the United States enters World War II, there is in prospect by an act of Congress a training program affecting millions of men over a period of at least five years. Unquestionably, the services of many thousands of physicians will be required in this training program. Indicative of the nature of the information to be supplied by *War Medicine* is the table of contents of the first issue:

Editorial:
War Medicine.

Industrial Hygiene and the Navy in National Defense. Ernest W. Brown, M.D., New York.

Amphetamine (Benzedrine) Sulfate: A Review of Its Pharmacology. A. C. Ivy, M.D., Ph.D., and L. R. Krasno, Ph.D., Chicago.

Aviation Medicine in the United States Navy. Frederick Ceres, M.D., Pensacola, Fla.

March Fracture: Report of Three Cases. Prentice L. Moore, M.D., and Allen N. Bracher, M.D., Schofield Barracks, Territory of Hawaii.

Official Statements:
Chemotherapy for Infectious Diseases and Other Infections: Circular Letter No. 81.

The Health and Medical Committee. E. H. Cushing, M.D., Cleveland.

Activities of the Medical Department in Augmentation of the Army: Official Statement from the Office of the Surgeon General of the United States Army.

The National Research Council and Medical Preparedness. Sanford V. Larkey, M.D., Baltimore.

A Census of Physicians for Military Preparedness. Rosco G. Leland, M.D., Chicago.

Preparedness with Drugs and Medicinal Chemicals. S. DeWitt Clough, Chicago.

Abstracts from Current Literature.

Book Reviews.

Material already available for forthcoming issues indicates that the American Medical Association is rendering a distinct service to our governmental medical departments, to the Division of Medical Sciences of the National Research Council and to the nation generally by the publication of this periodical.

MEDICAL PREPAREDNESS

In this section of The Journal each week will appear official notices by the Committee on Medical Preparedness of the American Medical Association, announcements by the Surgeon Generals of the Army, Navy and Public Health Service, and other governmental agencies dealing with medical preparedness, and such other information and announcements as will be useful to the medical profession.

ESTABLISHMENT OF A BOARD FOR THE INVESTIGATION OF INFLUENZA AND OTHER EPIDEMIC DISEASES IN THE ARMY

Following is a statement sent by Surgeon General James C. Magee to the Adjutant General on Dec. 27, 1940:

The present expansion of the Army has been accompanied by an increase in influenza and other acute respiratory diseases among troops. In certain localities these diseases have reached epidemic proportions, but fortunately they are still relatively mild and their mortality is low. However, if we may judge from the experience of previous mobilization, this comparatively favorable condition probably will not continue. As larger numbers of selectees are brought together, the rapid passage of infection from one individual to another will probably cause an increase in prevalence, virulence and fatal complications. In fact, the possibility cannot be ignored that the Army may again be confronted by another pandemic of influenza of the virulent type which caused such a large proportion of the total deaths among our troops during the last war.

During that period one of the important agencies utilized in the campaign against infectious diseases consisted of special boards composed of the most competent specialists available in the country, either military or civilian, whose function it was to study such conditions among troops and to advise the Surgeon General as to methods of prevention and treatment. An outstanding example was the "Pneumonia Board" appointed in 1918 (Special Order 118, W. D., May 20, 1918). This board, which met at irregular intervals in Washington at the call of the Surgeon General, not only rendered advisory service of inestimable value but organized and directed the studies of groups of expert epidemiologists, bacteriologists, chemists and pathologists, who were sent to certain camps and hospitals to investigate and combat this disease.

Since the World War our knowledge of the acute respiratory diseases has been increased enormously. We now know that certain of the interpandemic types of influenza are caused by filtrable viruses, and as these viruses can now be isolated it seems probable that eventually it may be possible to develop specific methods for their prevention. In view of the progress made recently in the study of these diseases, which are of such vital importance to the health and welfare of American troops, it is considered of urgent importance that the Army make immediate arrangements to utilize every scientific facility available in this country in a concerted effort to control these diseases and to reduce their mortality to a minimum.

With this objective in view, authority is requested for the Surgeon General to appoint and maintain a board for the investigation of the etiology, epidemiology, prevention and treatment of influenza and other acute epidemic diseases in the Army, this board to consist of such prominent physicians and other scientists as may be required from time to time, regardless of whether or not they are in the military establishment or other federal services or civilians not in the employ of the federal government. Because of the rapidity with which the respiratory diseases strike and the explosive nature of certain of the epidemics, it is essential that the organization of the board be made flexible and that its activities not be hampered by unnecessary administrative delays.

It is therefore recommended that this board be formed essentially as follows:

(*a*) *Organization and Personnel.*—That the board consist of (1) a central body of such scientists and technicists as may be required, which will meet at the call of the Surgeon General; (2) an additional group of such expert scientists and technicists as may be required as consultants, who will meet with the central body when called on individually by the president of the board; and (3) investigative teams, the number to be determined by the disease situation, each consisting of three or more scientists and technicists, who may be sent for temporary duty at military stations when deemed advisable by the Surgeon General for the study and control of epidemics. It is important that the total personnel for the board not be limited at this time but that it be subject to change from time to time as the Surgeon General may deem necessary to meet any emergency disease situation which may arise in the Army.

(*b*) *Status of Civilian Personnel.*—That the civilian members of the board who are not federal employees be paid transportation expenses and $20 a day while on temporary active duty at meetings or on investigative assignments with military organizations.

(*c*) *Procedure.*—That the central body of the board hold meetings from time to time, at times and places designated by the Surgeon General, in order to study the available current information concerning epidemic disease in the Army, and to formulate and recommend to the Surgeon General plans for its further study and control.

(*d*) *Control.*—That when the Surgeon General selects a team to investigate an epidemic at a military station the personnel of the team will be ordered to report to the proper local authority for temporary duty and will remain under that authority until the work is completed. The investigators will conduct their studies according to instructions from this office with as little interference as possible with the routine care of the sick. They will have the privilege of direct communication with the Surgeon General through technical channels on technical matters, and all other communications will be routed through regular military channels. A final report of the results of each investigation will be submitted to the Surgeon General through the main body of the board.

This establishment of this board will make available to the Army the scientific resources of the country to assist in the program for the control of influenza and the other epidemic diseases which will undoubtedly arise in our expanding army. Incidentally, its existence will undoubtedly be a matter of great satisfaction to the citizens of the country, who, remembering the tragic experience of the Army with influenza in 1918, are so vitally concerned over the possibility of a repetition of that experience. Therefore, from the viewpoint both of developing an effective agency for the study and control of this disease and the national morale, authority for the immediate formation of this board is urgently requested.

JAMES C. MAGEE,
Major General, U. S. Army,
the Surgeon General.

On Jan. 11, 1941, the plan was approved with the following memorandum:

War Department, A. G. O., January 11, 1941—To the Surgeon General.

The plan outlined in the basic letter for the establishment of a board for the investigation of influenza and other epidemic diseases in the Army is approved, except that civilian members of the board who are not federal employees will be paid not to exceed $20 per diem for any person so employed and necessary traveling expenses.

By order of the Secretary of War:

A. P. SULLIVAN, Adjutant General.

CHEMOTHERAPY FOR INFECTIOUS DISEASES AND OTHER INFECTIONS

CIRCULAR LETTER NO. 81

The data on which this circular letter is based have been prepared by the Committee on Chemotherapeutic and Other Agents and the Subcommittee on Infectious Diseases, of the Division of Medical Sciences, National Research Council. The Committee on Chemotherapeutic and Other Agents, chairman, Perrin H. Long, consists of Perrin H. Long, professor of preventive medicine, Johns Hopkins University School of Medicine, Baltimore; Francis G. Blake, professor of medicine, Yale University School of Medicine, New Haven, Conn.; John S. Lockwood, instructor in surgery, University of Pennsylvania School of Medicine, Philadelphia; J. F. Mahoney, senior surgeon, United States Public Health Service, Venereal Division, Research Laboratory, Staten Island, N. Y., and E. K. Marshall Jr., professor of pharmacology and experimental therapeutics, Johns Hopkins University School of Medicine, Baltimore. The subcommittee on infectious diseases, chairman, Francis G. Blake, consists of Francis G. Blake, professor of medicine, Yale University School of Medicine, New Haven, Conn.; Rolla E. Dyer, senior surgeon, United States Public Health Service, National Institute of Health, Washington, D. C.; Henry Helmholz, professor of pediatrics, University of Minnesota Graduate School, and the Mayo Clinic, Rochester, Minn.; Chester S. Keefer, professor of medicine, Boston University School of Medicine, Boston; Stuart Mudd, professor of bacteriology, University of Pennsylvania School of Medicine, Philadelphia, and Thomas M. Rivers, director of the Hospital of the Rockefeller Institute for Medical Research, New York.

In compliance with a request from the Surgeon General, the National Research Council appointed a committee to summarize the present status of chemotherapy with a view to its application in the treatment of military personnel. The following outline records briefly the opinions and recommendations of that committee concerning infections and infectious diseases. Because of the rapid development of chemotherapeutic agents, it is likely that some of these recommendations will have to be modified from time to time. Certain measures other than chemotherapeutic are described briefly when it seems appropriate. However, it is impracticable, except in a broad way, to delineate the therapy of persons suffering from various infections. This outline is published, therefore, as a general guide for medical officers and is to be used at their discretion, with due consideration of all other factors which may be presented by each individual case. It is not intended that it will be used to the exclusion or neglect of other indicated therapeutic or nursing procedures.

The Medical Department will continue to supply therapeutic serums for patients who are sensitive to chemotherapeutic agents and for those who in the opinion of the responsible medical officer may be advantageously treated with such serums.

Therapy for the following conditions is discussed: (1) hemolytic streptococcus infections, (2) scarlet fever, (3) meningococcic meningitis, (4) purulent meningitis, (5) pneumonia, (6) gas bacillus infections and (7) staphylococcic infections.

This official statement appeared in War Medicine **1**: 55 (Jan.) 1941.

HEMOLYTIC STREPTOCOCCUS INFECTIONS

(*a*) *Mild or Moderately Severe Hemolytic Streptococcus Infections, Such as Erysipelas; Mild Cellulitis and Tonsillitis.*

Specific treatment:

Sulfanilamide: Recommended as the drug of choice. Initial dose (oral): 2 Gm. Subsequent doses: 1 Gm. every four hours day and night, until five days of normal temperature have elapsed. (The subsequent dosage may be modified after forty-eight hours of normal temperature at the discretion of the medical officer.) Then stop the use of the drug.[1]

(*b*) *Otitis Media.*—This condition is generally caused by hemolytic streptococci but may be caused by pneumococci or other organisms and presents a special case. Treatment should be started as outlined in the foregoing section; bacteriologic cultures should be made and if the infecting organism turns out to be a pneumococcus or a staphylococcus sulfathiazole should be substituted, the dose being 1 Gm. every four hours, day and night, until the patient's temperature has been normal for five days. Therapy should be continued by giving small doses, of 0.5 Gm. four times daily, for at least ten days after a *clinical* cure has been effected.

(*c*) *Severe Hemolytic Streptococcus Infections, Such as Meningitis, Septicemia, Severe Cellulitis, Acute Osteomyelitis and Acute Mastoiditis.*

Specific treatment:

Sulfanilamide: Recommended as the drug of choice. Initial dose (oral): 6 Gm. Subsequent doses: 1 Gm. every four hours, day and night, until the temperature has been normal for seven days. For acute streptococcic mastoiditis or osteomyelitis, administration of sulfanilamide should be continued in small doses of 0.5 Gm. four times daily for at least ten days after a *clinical* cure has been effected.

SCARLET FEVER

(*a*) *Active Immunization with Toxin.*—This procedure is not recommended for the following reasons:

1. High percentage of immune subjects among adults.
2. Five or more injections of toxin are usually required to produce immunity.

Exception: Active immunization should be used for nurses with positive reactions to Dick tests and for orderlies assigned to care for patients with scarlet fever.

(*b*) *Simple Toxic Scarlet Fever (Exanthematous Stage).*

Specific treatment:

1. Antitoxin: Recommended in all cases in which the disease is moderately severe to extremely severe and the patient is not hypersensitive to horse serum.[2]

1. The routine use of sodium bicarbonate is unnecessary in treatment with sulfanilamide and its derivatives. This applies wherever such therapy is recommended in this circular letter.

2. Serum should never be given to patients who have a history of asthma of any type or to those who have a history of hay fever. Whenever serum is administered, have a syringe containing 1 cc. of epinephrine hydrochloride, 1 to 1,000 solution, at the bedside of the patient in order that this drug may be injected rapidly if an anaphylactic reaction develops. Two tests for serum sensitivity are available, and it is frequently desirable to use both. The first consists of the intracutaneous injection of 0.1 cc. of a solution of the serum diluted 1 to 10 in sterile physiologic solution of sodium chloride. The reaction is positive if at the end of twenty minutes the wheal at the site of the injection has enlarged to the size of a nickel and has an area of redness about it. The second test is the conjunctival test. This consists of instilling 1 drop of a 1 to 10 dilution of the serum in sterile physiologic solution of sodium chloride inside the lower eyelid of the patient. If redness and swelling of that eye appear within twenty minutes, the reaction is positive. A positive reaction can be countered easily by instilling 1 or 2 drops of a 1 to 1,000 solution of epinephrine hydrochloride inside the lower eyelid, a procedure which should be followed with all positive reactors in order to prevent the rare instances of corneal ulceration. These tests are interpreted as follows: 1. If the ophthalmic and cutaneous reactions *(Continued on page 514)*

The antitoxin should be given in one dose as soon as the diagnosis is made, intramuscularly if the disease is moderately severe and intravenously if it is severe to extremely severe, according to the following schedule: moderately severe, 18,000 units; severe, 27,000 to 36,000 units, and very severe, 45,000 units.

2. Sulfanilamide: No therapeutic effect on the toxic stage. It should be used for prophylaxis of septic complications in the dosage of 0.5 Gm. four times daily for the period of quarantine.

(*c*) *Toxic and Septic Scarlet Fever (Exanthematous Stage).*

Specific treatment:

1. Antitoxin (globulin concentrated): Recommended as stipulated in the foregoing section. Patients with early septic lesions (purulent rhinopharyngitis, sinusitis, otitis media, mastoiditis or marked lymphadenitis, and so on) in general are actually or potentially more toxic than patients with simple toxic (uncomplicated) scarlet fever. The doses used should be larger, according to the following schedule: if the disease is moderately severe, 27,000 units; if severe, 45,000 units, and if very severe, 63,000 units.

2. Sulfanilamide: Recommended in addition to antitoxin for its chemotherapeutic effect on septic lesions. Initial dose: 6 Gm. Subsequent doses: 1 Gm. every four hours, day and night, until the temperature has been normal for five days; then 0.5 Gm. four times daily for the period of quarantine.

(*d*) *Late Septic Complications (Postexanthematous Stage).*

Specific treatment:

1. Antitoxin: Of no value; not recommended.

2. Sulfanilamide: Recommended; dosage and duration of treatment as given in the foregoing section.

(*e*) *Precautions.*

1. Antitoxin: The usual precautions employed in giving horse serum should always be used.[2] Serum disease may be expected in approximately 25 per cent of cases.

2. Sulfanilamide: Symptoms and signs of acute hemolytic anemia, neutropenia, drug fever, dermatitis and hepatitis should be watched for carefully and sulfanilamide stopped at once if they appear. (See also the last section of this circular letter, on toxic effects of drugs.)

MENINGOCOCCIC MENINGITIS

Specific treatment:

1. Serum: It is generally recommended that antimeningococcus serum should not be used in the treatment of meningococcic meningitis. However, in individual cases, serum may be used if in the opinion of the medical officer it is indicated.

2. Chemotherapy: Sulfanilamide: Recommended as the drug of choice. The intrathecal administration of this drug is not indicated. Initial dose (oral): 6 Gm. Subsequent doses: 1 Gm. every four hours, day and night, until the temperature has been normal for seven days. Lumbar puncture is indicated only for diagnosis and subsequently only to relieve manifestations of increased intracranial pressure.

PURULENT MENINGITIS

In case the cause of a purulent meningitis is not promptly established, chemotherapy should, nevertheless, be instituted at once with sulfapyridine as follows:

Initial dose (oral): 4 Gm. Subsequent doses: 1 Gm. every four hours, day and night, until the temperature has been normal for seven days.

Sodium sulfapyridine should be used intravenously if oral treatment is impossible. If it is used, the initial dose is 0.06 Gm. per kilogram of body weight, made up in a 5 per cent solution in sterile, freshly distilled water. This solution is given slowly (fifteen minutes) by the intravenous route, care being taken not to get the alkaline material outside the vein, because if this occurs it will cause a slough. Solutions of sodium sulfapyridine should never be added to transfusion blood, solutions of sodium chloride or dextrose or other fluids for intravenous use. Subsequent doses should be calculated on the basis of 0.03 Gm. per kilogram of body weight and should be given by the intravenous route at six hour intervals; oral therapy with sulfapyridine should be started as soon as it is practicable.

PNEUMONIA

The specific prophylaxis and treatment of pneumonia are based on etiologic classification and diagnosis, which should be carried out promptly in all cases whenever laboratory diagnostic facilities are available.

Pneumonia is classified in two main groups: (1) primary, which occurs independently of any major predisposing cause, and (2) secondary, which occurs as a complication of a major predisposing cause, e. g. influenza, measles or pertussis.

Primary pneumonia is principally caused by the pneumococcus. Other bacteria, e. g. Streptococcus haemolyticus (beta), staphylococcus or Friedländer's bacillus, may occasionally be the cause.

Secondary pneumonia complicating such diseases as influenza or measles is of variable etiology, often mixed, sometimes indeterminate. The higher types of pneumococci, beta hemolytic streptococci and Haemophilus influenzae are the bacteria most frequently concerned. Staphylococci, the gram-negative micrococci and Str. viridans may be found.

(*a*) *Primary Pneumonia.*

1. Pneumococcic pneumonia (usually lobar).

Chemotherapy: Recommended as the method of choice in all cases for the following reasons: (1) highly effective, except in the aged with chronic disease; (2) effective against all types of pneumococci; (3) may be given at once without waiting for type determination; (4) administration technically simple and relatively inexpensive, and (5) also applicable to treatment of most bacterial pneumonia other than pneumococcic.

Sulfathiazole is recommended as the drug of choice in all cases for the following reasons: (1) greatly superior to sulfanilamide in scope and effectiveness of therapeutic action; (2) at least equivalent to sulfapyridine in scope and effectiveness of therapeutic action; (3) causes much less nausea, vomiting and mental disturbance than sulfapyridine; (4) other untoward reactions are (probably) less frequent and less severe than with sulfapyridine, and (5) the problem of excessive acetylation is not encountered to the same degree as it is with sulfapyridine.

Administration of sulfathiazole should be started at once in all cases as soon as the clinical diagnosis is made, etiologic diagnosis being carried out at the same

are negative, then antitoxin may be given by any route. 2. A definite wheal-like reaction, with surrounding erythema, indicates cutaneous sensitivity. 3. A positive ophthalmic reaction, with or without a positive intradermal reaction, indicates a probable systemic reaction. Serum should never be given if both the ophthalmic and the cutaneous reactions are positive and should be used only with the greatest of care if either the ophthalmic or the cutaneous reaction is positive. This warning also applies to the serum treatment of meningococcic meningitis, pneumococcic pneumonia and gas bacillus infections.

time. Initial dose (oral): 4 Gm. Subsequent doses: 1 Gm. every four hours, day and night, until the temperature has been normal for seventy-two hours. In cases in which the disease is very severe, an initial dose of sodium sulfathiazole (5 per cent solution in sterile distilled water), amounting to 0.06 Gm. per kilogram of body weight, may be given *intravenously*. To patients unable to take sulfathiazole by mouth, intravenous treatment with sodium sulfathiazole (5 per cent solution in sterile distilled water) should be given. (The solution of sodium sulfathiazole need not be sterilized.) The initial dose of sodium sulfathiazole should be 4 Gm. Subsequent doses of 2 Gm. each should be given every six hours. Oral administration should be instituted as soon as possible.

bacteremia. If these amounts prove insufficient, subsequent doses of 100,000 units each should be given every eight hours.

Precautions: Force fluids to 3,500 cc. a day. The usual precautions employed in all intravenous serum therapy should be observed. Serum should not be given to hypersensitive persons.[2]

2. Hemolytic streptococcic pneumonia, Friedländer's bacillus pneumonia and staphylococcic pneumonia.

Sulfathiazole: Recommended in all cases. Method of treatment same as for pneumococcic pneumonia. Initial dose (oral): 4 Gm. Subsequent doses (oral): Begin with 1 Gm. every four hours; if response is not satisfactory, increase to 1.5 to 2 Gm. every four hours until improvement is definite; then reduce to 1 Gm.

*Manifestations of Toxicity Due to Drugs Noted in Hospitalized Patients**

Reaction	Drug		
	Sulfanilamide	Sulfapyridine	Sulfathiazole
Nausea and vomiting.....	Fairly common	Frequent	Uncommon
Dizziness.....	Common	Common	Uncommon
Psychosis †.....	In 0.6% of cases; occurs early	In 0.3% of cases, occurs early	Very rare
Neuritis †.....	Very rare	Not reported	Rare
Cyanosis.....	Very common; occurs early and late	Faint; common; occurs early and late	Uncommon
Acidosis †.....	In 1.9% of cases; occurs at any time	Not reported	Not reported
Fever †.....	In 10% of cases, generally occurs on 5th to 9th day; may occur on 1st to 30th day	In 4% of cases, generally occurs on 5th to 9th day; may occur on 1st to 30th day	In 10% of cases, generally on 5th to 9th day
Rash †.....	In 1.9% of cases; may take any form; generally occurs on 5th to 9th day; may occur on 1st to 30th day	In 2% of cases; may take any form; generally occurs on 5th to 9th day; may occur on 1st to 30th day	5% of cases; nodular type common; may take any form; occurs on 5th to 9th day
Hepatitis ‡.....	In 0.6% of cases; occurs early or late	Not noted but reported	Rare
Leukopenia with granulocytopenia ‡	In 0.3% of cases; occurs early or late	In 0.6% of cases; occurs early or late	In 1.6% of cases; occurs early or late
Agranulocytic angina ‡...	In 0.1% of cases; occurs on 14th to 40th day; more frequent on 17th to 25th day	In 0.3% of cases; occurs on 14th to 40th day; more frequent on 17th to 25th day	Not reported but may occur
Mild hemolytic anemia....	In 3.0% of cases; occurs early and late	Rare	Not reported
Acute hemolytic anemia ‡	In 1.8% of cases; occurs on 1st to 5th day	In 0.6% of cases; occurs on 1st to 5th day	Very rare
Hematuria †.....	Not reported	In 8% of cases; generally occurs early	In 2.5% of cases; generally occurs early
Anuria with azotemia ‡...	Not reported	In 0.3% of cases; generally occurs during first ten days	In 0.7% of cases; generally occurs during first ten days
Hyperleukocytosis †.....	Generally in presence of acute hemolytic anemia	Generally in presence of acute hemolytic anemia	Not reported
Injection of scleras and conjunctivas †	Not reported	Not reported	In 4.0% of cases; may occur with rash and fever; occurs on 5th to 9th day
Purpura haemorrhagica ‡	Not seen but reported	Not seen but reported	Not reported
Ocular and auditory disturbances †	Rare	Rare	Rare
Jaundice ‡.....	With acute hemolytic anemia or hepatitis	With acute hemolytic anemia or hepatitis	Rare
Painful joints †.....	Reported	Not reported	Reported, with rash
Stomatitis †.....	Rare	Not reported	Not reported
Disturbances in gastrointestinal tract †	Bleeding rare; diarrhea uncommon	Rare	Not reported

* The patients were adults: 1,000 were treated with sulfanilamide, 291 with sulfapyridine, and 271 with sulfathiazole.
† A sign that it is best to stop the drug and force fluids.
‡ A sign that it is imperative to stop the drug and force fluids.

Serum therapy: Homologous type antipneumococcus serum, preferably rabbit serum, recommended in addition to sulfathiazole therapy for: (1) patients with early stages of the disease (seventy-two hours after onset) only when they have failed to show satisfactory response to forty-eight hours of chemotherapy (this happens rarely) and (2) patients with late stages of the disease (seventy-two hours after onset), clinically unusually severe, who presumptively have bacteremia or who have failed to respond to chemotherapy alone.

Method of treatment: If the patient is not hypersensitive to serum (see footnote 2), it is recommended that an initial dose of 200,000 units of antipneumococcus rabbit serum of homologous type be given intravenously to patients with early stages of the disease who have not responded to chemotherapy and an initial dose of 300,000 units to those with late stages of the disease, in a severe form, who presumptively have

every four hours and continue until the temperature has been normal for five days.

Sodium sulfathiazole: Same as in cases of pneumococcic pneumonia.

Precautions: Same as those taken in cases of pneumococcic pneumonia.

(*b*) *Secondary Pneumonia.*

Prophylaxis: The possible value of chemotherapy with sulfanilamide and its derivatives in the prevention of bacterial pneumonia complicating such diseases as influenza and measles is not known at present. Specific recommendations are therefore not justified.

Chemotherapy: Sulfathiazole is recommended in all cases in which pneumococci, hemolytic streptococci, staphylococci or Friedländer's bacilli are found and believed to be of etiologic significance. The method of treatment, the dosage and the precautions are the same as in cases of primary pneumonia.

Comment: Chemotherapy with sulfanilamide and its derivatives is of no demonstrated value for many patients with bronchopneumonia of indeterminate (virus?) etiology; it is also of no demonstrated value against pulmonary infections with Str. viridans or Haemophilus influenzae. Results in treating secondary pneumonia, which is often due to a mixed infection, will, therefore, be variable, often disappointing and difficult to evaluate, even when bacteria known to be susceptible to the action of the sulfanilamide compounds are present in the patient's sputum.

GAS BACILLUS INFECTIONS

It is recommended that all rational surgical procedures, such as débridement, be carried out as soon as possible and that all necessary supportive treatment be administered.

(*a*) *Serum Therapy.*

In the light of present knowledge concerning the value of polyvalent tetanus-gas bacillus antitoxin in the prophylaxis and treatment of gas gangrene, it is recommended that the prophylactic and therapeutic use of these serums be considered when in the opinion of the attending medical officer their use for a given patient is indicated.

Prophylactic dosage: Polyvalent tetanus-gas gangrene antitoxin 5,500 units.

Therapeutic dosage: 20,000 to 40,000 units or more given intravenously, supplemented, if need be, by intramuscular injections. These doses may be repeated in from twelve to twenty-four hours, depending on the symptoms and the response of the patient to the initial dose.

(*b*) *Chemotherapy.*

(1) Prophylaxis: Sulfanilamide recommended *at present* as the drug of choice. Initial dose (oral): 6 Gm. Subsequent doses: 1 Gm. every four hours, day and night, for seven days or until definitive treatment is available. This period of therapy almost always eliminates the possibility of gas bacillus infection.

(2) Treatment: Sulfanilamide recommended *at present* as the drug of choice. Initial dose (oral): 6 Gm. Subsequent doses: 1 Gm. every four hours, day and night, should be given until the temperature has been normal for forty-eight hours; then 0.5 Gm. every four hours, day and night, until convalescence is completely established.

Crystalline sulfanilamide may be used *locally*, 0.1 Gm. per square inch of treated surface.

STAPHYLOCOCCIC INFECTIONS

(*a*) *Localized Boils and Carbuncles.*

(1) Small furuncles: Apply hot wet dressings until definite fluctuation develops. Lesions which do not evacuate themselves spontaneously after becoming fluctuant should be promptly incised and drained. Chemotherapy is not recommended for these minor staphylococcic infections.

(2) Large boils and carbuncles: Administer sulfathiazole in an initial dose of 4 Gm. and 1 Gm. every four hours thereafter for seven days. Apply hot fomentations. Incise as necessary after fluctuation develops in order to encourage the evacuation of necrotic slough. Avoid incision of uninfected tissue or of diffuse cellulitis.

(*b*) *Diffuse Cellulitis, Lymphangitis and Acute Osteomyelitis.*

1. Immobilize the infected part in a splint and elevate it continuously.

2. Apply bulky gauze dressing, wet with saline solution, and keep dressing warm, if possible.

3. Give sulfathiazole: Initial dose: 4 Gm., followed by 1.5 Gm. every four hours thereafter. Continue use of the drug at this dose level as long as evidence of spreading infection continues; then reduce the dose to 1 Gm. every four hours and continue for at least seven days.

4. Employ surgical treatment for any areas of localized suppuration which may develop.

(*c*) *Staphylococcic Bacteremia.*

1. Give sulfathiazole: Initial dose: 4 Gm., followed by 1.5 Gm. every four hours until the patient's temperature has been normal for forty-eight hours. Then reduce the dose to 1 Gm. every four hours and continue at this level for fourteen days. The likelihood of relapse is great unless prolonged, continuous chemotherapy is employed.

2. Make every effort through careful clinical and roentgen examination to identify foci of distribution and localization. These should be treated by surgical drainage if they are accessible. Sulfathiazole may control invasive manifestations of infection but will not, by itself, bring about a cure of areas of localized infection, and reinvasion from such areas is likely if they are not drained.

(*d*) *Chronic Staphylococcic Suppuration (as in Chronic Osteomyelitis).*

1. Maintain drainage by packing with petrolatum gauze to the depths of the wound until sequestration of necrotic bone and tissue has occurred and the wound is covered with clean granulations.

2. Oral administration of sulfathiazole is not of much value. Local application of powdered sulfathiazole may be helpful but is still in the experimental stage and cannot be definitely recommended.

TOXIC EFFECTS FROM ADMINISTRATION OF DRUGS

In the table are listed some of the toxic effects which have been noted when treatment with sulfanilamide or one of its derivatives has been employed.

It is to be recommended that when possible laboratory control of bacterial chemotherapy be carried out, but inability to do examinations of the blood and urine should never be considered a contraindication to the use of the sulfanilamide compounds. If facilities are available, hemoglobin determinations should be done every other day during the first week of treatment and once a week thereafter. Total and differential white blood cell counts should be done every other day for the first seven days and (particularly important) if the patient continues treatment with sulfanilamide or its derivatives, every two days between the fourteenth and the fortieth day. Examinations of the urine should be done on alternate days for patients who are receiving sulfapyridine or sulfathiazole. The urine should be examined microscopically for blood. The output of urine of patients being treated with sulfathiazole or sulfapyridine for serious infections should be recorded daily. Patients receiving sulfanilamide compounds should be seen at least once a day and should be questioned as to the presence of headache or malaise. These are frequently important early symptoms of toxic reactions. Patients should be inspected at each visit for the presence of jaundiced scleras (acute hemolytic anemia or hepatitis), pale mucous membranes (acute hemolytic anemia) or rash. The temperature should be recorded. *If fever occurs after the patient's temperature has been normal in the course of treatment with*

sulfanilamide or one of its derivatives, the drug should be discontinued immediately or if recently discontinued should not be resumed unless it has been demonstrated that the fever is due to a recurrence of the infection. Whenever therapy with the sulfanilamide drugs is stopped because of a drug reaction, *fluids should be forced so that 5,000 cc. a day is taken in order to wash out the drug.*

Agranulocytosis is extremely rare before the fourteenth day of therapy. It is imperative that total and differential white cell counts be made for patients still under treatment after the fourteenth day, every two days from the fourteenth to the fortieth day. If the percentage of polymorphonuclear leukocytes falls to 50 per cent or less in an adult patient, the drug should be stopped immediately. Granulocytopenia without acute agranulocytosis may occur.

Any patient who has had a toxic reaction to one of the sulfanilamide group of drugs may have a second, and more severe, reaction if one of these drugs is prescribed again. To such patients a small test dose of the drug (0.1 to 0.3 Gm.) should be given and the patient observed for twelve hours before intensive therapy is started, following which the patient must be carefully observed and the drug immediately stopped on the first appearance of any toxic manifestation.

SYMPOSIUM ON MILITARY MEDICINE

The California Medical Association and the San Diego County Medical Society sponsored a symposium on military medicine in San Diego February 1-2, under the chairmanship of Captain Chambers, commanding officer, U. S. Naval Hospital, who was supported by Capt. John D. Manchester, U. S. Navy, medical corps, retired; Rear Admiral Charles A. Blakeley, commandant of the eleventh naval district, and Major General William P. Upshur, commandant of the marine base. The speakers were:

Dr. Harry H. Wilson, Los Angeles, Greetings from the State Medical Association.

Dr. Philip K. Gilman, San Francisco, Status of Medical Preparedness in California.

Lieut. Col. Bert S. Thomas, Sacramento, Selective Service Plans in California.

Capt. William L. Mann, Combined Operations of Naval Medical Department Unit with Land and Sea Forces.

Capt. Griffith E. Thomas, The Medical Side of Naval Recruit Training.

Capt. Frederic L. Conklin, Surgery in Modern Warfare.

Comdr. Louis H. Roddis, The Training of Hospital Corpsmen in the Navy.

Comdr. Joel J. White, Some Aspects of Aviation Medicine.

Comdr. Eugene L. Walter, The Dental Side of Naval Recruit Training.

Lieut. Comdr. John F. Luten, Venereal Diseases and National Defense.

MEETINGS OF INDUSTRIAL HYGIENISTS

The annual meeting of the National Conference of Governmental Industrial Hygienists will be held in Bethesda, Md., February 17-18 rather than in May in order to develop a coordinated industrial hygiene program for defense industries. The conference will discuss ways in which the state industrial hygiene units, the Division of Industrial Hygiene and the Subcommittee on Industrial Health and Medicine can cooperate most effectively in maintaining and improving the health of employees in industries producing materials essential to the national defense.

The Rocky Mountain Industrial Hygienists will hold a conference in Idaho Falls, Idaho, the early part of February, for the purpose of discussing industrial hygiene problems, especially as they relate to national defense. Representatives from Utah, Colorado, Wyoming, Montana and Idaho will participate in the conference.

NURSES NEEDED FOR IMMEDIATE ASSIGNMENT

The War Department has announced that three hundred and twenty-five nurses are needed for assignment by February 15 to staff the hospital at the following training centers, which will be occupied by troops by the early part of March:

Fort Devens, Mass., First Division, Regular Army, one hundred and twenty nurses.

Indiantown Gap Military Reservation, Pa., Twenty-Eighth Division, Pennsylvania National Guard, eighty-five nurses.

Camp Forrest, Tenn. (formerly Camp Peay), Thirty-Third Division, Illinois National Guard, one hundred and twenty nurses.

To be eligible for commission in the Army Nurse Corps Reserve, nurses must be single, American citizens, between the ages of 21 and 40, and must be graduates of approved nursing schools which are registered as provided by state laws. The initial rate of pay is $70 a month with full maintenance. Information may be obtained by writing to the Surgeon General, U. S. Army, Washington, D. C.

LIBRARY ON MILITARY MEDICINE PRESENTED TO YALE

Dr. John F. Fulton, Sterling professor of physiology, Yale University School of Medicine, New Haven, Conn., has presented to the Yale Medical Library a collection of all books and government documents bearing on military medicine published in England since the beginning of the war. There are about fifty items in the group plus a collection of all the reports of the Medical Research Council on various phases of industrial medicine. In the latter series there are about seventy titles. The collection is now available in the new Reading Room of the General Medical Library in the Sterling Hall of Medicine.

PHARMACEUTICALS TO BRITAIN

The Western New York branch of the American Pharmaceutical Association recently conducted a campaign to collect drugs and medicinal preparations to send to England. Donations included one million aspirin tablets from one manufacturer, 7,500 tablets of sulfanilamide from another, varying amounts of vitamin preparations and supplies such as gauze, adhesive tape, hypodermic needles, cotton, rubber gloves and antiseptics. Pharmacy students at the University of Buffalo collected the donations as their contribution to the campaign.

LITERATURE ON MILITARY MEDICINE

The library of the Medical Society of the County of Kings, New York, has compiled a list of its publications on military, naval and aviation medicine. The list includes more than fifty books, manuals, pamphlets and reprints. In addition, the library keeps on file a number of current periodicals devoted wholly or partly to military medicine.

MORE HOSPITAL FACILITIES AT FORT SHERIDAN

The War Department authorized, January 7, the construction of additional hospital facilities at Fort Sheridan, Illinois, which will provide from one hundred and eighty-four to two hundred and sixty-nine additional beds and cost about $295,500.

LECTURES ON MEDICAL PREPAREDNESS

The Philadelphia County Medical Society has begun its second series of lectures on medical preparedness, arranged by the committee on national defense. At the first meeting, January 30, Drs. Baldwin L. Keyes and Edmund B. Spaeth discussed "Malingering" from the point of view of the psychiatrist and the ophthalmologist respectively. The committee plans to arrange monthly lectures.

ARMY RESERVE OFFICERS ORDERED TO ACTIVE DUTY

THIRD CORPS AREA

The following additional medical reserve corps officers had been ordered to extended active duty by the Commanding General, Third Corps Area, up to January 24. The Third Corps Area comprises the states of Pennsylvania, Virginia, District of Columbia and Maryland.

BOWERS, George Steel, 1st Lieut., Rustburg, Va., Fort George G. Meade, Md.
CHALFANT, Chads Owen, 1st Lieut., Donora, Pa., Fort Belvoir, Va.
ENGLEHART, Charles Edward, Captain, Edgewood, Pa., Fort Myer, Va.
FERKANY, Joseph Ernest, 1st Lieut., McKees Rocks, Pa., Fort McClellan, Ala.
JAVOIS, Alexander John, Captain, Pittsburgh, Camp Lee, Va.
JENNINGS, Edward Clifford, 1st Lieut., Washington, D. C., Indiantown Gap, Pa.
KEITHAN, John Frederick, 1st Lieut., Doylestown, Pa., Camp Lee, Va.
LEONE, Peter Pascal, 1st Lieut., Philadelphia, Camp Blanding, Fla.
McGILL, John Francis, 1st Lieut., Pittsburgh, Camp Shelby, Miss.
McLANE, Charles Francis, Jr., 1st Lieut., South Williamsport, Pa., Camp Lee, Va.
McNELLIE, William Owen, 1st Lieut., Pittsburgh, Camp Blanding, Fla.
MESSER, William Allison, Captain, Pittsburgh, Fort George G. Meade, Md.
ORLEANS, Harry Byron, Captain, Washington, D. C., Fort Belvoir, Va.
PEACOCK, John Howell, Jr., 1st Lieut., Washington, D. C., Fort Belvoir, Va.
POHL, Charles Matthew, 1st Lieut., Manheim, Pa., Edgewood Arsenal, Md.
SMITH, John Prinz, 1st Lieut., Baltimore, Camp Lee, Va.
SOMMERS, Elmo Bauer, 1st Lieut., Norristown, Pa., Camp Blanding, Fla.
WHITLEY, Ayer Crouch, Captain, Palmyra, Va., Camp Shelby, Miss.
WOODWARD, Theodore Englar, 1st Lieut., Westminster, Md., Fort George G. Meade, Md.

FOURTH CORPS AREA

The following additional medical reserve corps officers have been ordered to active duty by the Commanding General, Fourth Corps Area, since January 17. The Fourth Corps Area comprises the states of Tennessee, North Carolina, South Carolina, Alabama, Georgia, Mississippi, Florida and Louisiana.

BATES, Thomas H., Major, Lake City, Fla., Fort Benning, Ga.
CAMP, Benjamin L., Captain, Ellijay, Ga., Fort Bragg, N. C.
CARTER, Harvey W., 1st Lieut., Murfreesboro, Tenn., Fort Sam Houston, Texas.
COLLUM, Tillman B., 1st Lieut., Golden, Miss., Fort Benning, Ga.
COUSAR, John B., 1st Lieut., Bishopville, S. C., Fort Jackson, S. C.
CULLIPHER, Edward W., Captain, Miami, Fla., Fort Benning, Ga.
DuBARD, Horton G., 1st Lieut., Knoxville, Tenn., Camp Peay, Tenn.
ELLIOTT, John L., Captain, Savannah, Ga., Fort Benning, Ga.
FARRER, Frederick E., 1st Lieut., Miami, Fla., Camp Wheeler, Ga.
FELDNER, George D., Major, New Orleans, Fort Benning, Ga.
GORMAN, John M., Major, Jacksonville, Fla., Fort Benning, Ga.
JAMES, Samuel W., 1st Lieut., Ackerman, Miss., Fort Benning, Ga.
KENDRICK, Odis G., Major, Tallahassee, Fla., Fort Benning, Ga.
KENNEDY, David W., 1st Lieut., Vivian, La., Fort Bragg, N. C.
KINNARD, George P., Major, Newman, Ga., Fort Benning, Ga.
LEA, Joseph D., 1st Lieut., Baton Rouge, La., Camp Claiborne, La.
LIPSCOMB, James E., Jr., 1st Lieut., Greenville, S. C., Fort Bragg, N. C.
MANASCO, Hobson, 1st Lieut., Carbon Hill, Ala., Camp Croft, S. C.
McDANIEL, Thomas F., 1st Lieut., Sanford, Fla., Fort Benning, Ga.
McELHENY, Franklin, 1st Lieut., Miami, Fla., Fort Bragg, N. C.
MORIN, Henri G., 1st Lieut., St. Petersburg, Fla., Fort Benning, Ga.
NEUFFER, Frank H., 1st Lieut., Atlanta, Ga., Fort Beninng, Ga.
PROVOST, Edwin K., 1st Lieut., Nashville, Tenn., Fort Benning, Ga.
QUANTZ, Herman C., 1st Lieut., Shreveport, La., Fort Benning, Ga.
RAINES, Hugh R., Major, Memphis, Tenn., Fort Benning, Ga.
ROSENBAUM, Maurice M., Captain, Shallotte, N. C., Fort Sam Houston, Texas.
SHERMAN, Kenneth G., Captain, Biloxi, Miss., Camp Davis, N. C.
SMITH, George C., 1st Lieut., Florence, S. C., Camp Peay, Tenn.
SNEED, Ralph, 1st Lieut., Jackson, Miss., Camp Davis, N. C.
TATUM, Walter L., Lieut. Col., Salisbury, N. C., Fort Benning, Ga.
WARD, Albert L., 1st Lieut., Fort St. Joe, Fla., Fort Benning, Ga.
WEINSTEIN, Howard I., 1st Lieut., Sumter, S. C., Fort Benning, Ga.
WILSON, Samuel A., 1st Lieut., Lincolnton, N. C., Camp Beauregard, La.

Relieved from Duty

The following officers, previously reported, have been relieved from duty or their orders have been revoked:

HIGHTOWER, Jesse R., 1st Lieut., Itta Bena, Miss.
NORMENT, Robert L., 1st Lieut., Lumberton, N. C.

SIXTH CORPS AREA

The following additional medical reserve officers had been ordered to extended active duty by the Commanding General, Sixth Corps Area, up to January 24. The Sixth Corps Area comprises the states of Wisconsin, Illinois and Michigan.

BAUER, Gerhard H., 1st Lieut., Ann Arbor, Mich., 5th Division, Fort Custer, Mich.
BOUYER, Harsba F., 1st Lieut., Chicago, 184th Field Artillery, Fort Custer, Mich.
BRISTOW, Jack H., 1st Lieut., Monroe, Wis., 5th Division, Fort Custer, Mich.
BROWN, King D., Captain, Chicago, 184th Field Artillery, Fort Custer, Mich.
BROWN, Marion G., 1st Lieut., Detroit, 38th Infantry, Fort Sam Houston, Texas.
BROWNS, Herschel L., 1st Lieut., Ann Arbor, Mich., Medical Supply Depot, Fort Sam Houston, Texas.
CALLAHAN, George B., Captain, Waukegan, Ill., 2d Medical Laboratory, Fort Sam Houston, Texas.
CAMPBELL, William J., 1st Lieut., Detroit, Medical Supply Depot, Fort Sam Houston, Texas.
COOK, James C., 1st Lieut., Detroit, Station Hospital, Fort Custer, Mich.
CROSS, Kenneth R., 1st Lieut., Detroit, 5th Division, Fort Custer, Mich.
CROUT, George T., Captain, Flanagan, Ill., 2d Medical Laboratory, Fort Sam Houston, Texas.
DEUTERMAN, Joel L., Captain, Elgin, Ill., Station Hospital, Camp Grant, Ill.
DOUD, Ernest A., 1st Lieut., Chicago, 5th Division, Fort Custer, Mich.
FINKLE, John R., Major, Plainfield, Ill., 77th Field Artillery, Fort D. A. Russell, Wyo.
GARLAND, John C., Captain, Mount Carroll, Ill., Medical Supply Depot, Fort Sam Houston, Texas.
GORDON, Orville E., 1st Lieut., Chicago, 5th Division, Fort Custer, Mich.
GUZZETTA, Marcus M., 1st Lieut., Milwaukee, Medical Supply Depot, Fort Sam Houston, Texas.
HERSOG, Paul, 1st Lieut., Kenosha, Wis., 1st Medical Squadron, Fort Bliss, Texas.
HOERNSCHMEYER, Joseph L., Captain, Granite City, Ill., 2d Medical Laboratory, Fort Sam Houston, Texas.
HOUSTON, William H., 1st Lieut., Ann Arbor, Mich., 1st Medical Squadron, Fort Bliss, Texas.
IMMERMAN, Harold M., 1st Lieut., Saginaw, Mich., 2d Medical Battalion, Fort Sam Houston, Texas.
KAISER, Lloyd F., 1st Lieut., Rhinelander, Wis., Medical Supply Depot, Fort Sam Houston, Texas.
KEHL, Sylvester C., Major, Chicago, Medical Supply Depot, Fort Sam Houston, Texas.
KINGSBURY, Charles H., 1st Lieut., Goodman, Wis., 1st Medical Squadron, Fort Bliss, Texas.
KNAPP, Howard C., Captain, Belleville, Ill., 2d Medical Laboratory, Fort Sam Houston, Texas.
KNEWITZ, Ralph W., Captain, East St. Louis, Ill., 12th Cavalry, Fort Ringgold, Texas.
KNUTSON, Lewis A., 1st Lieut., Westby, Wis., 1st Medical Squadron, Fort Bliss, Texas.
KRETLOW, Fred A., 1st Lieut., Chicago, 1st Medical Squadron, Fort Bliss, Texas.
LEPAK, Alfred J., 1st Lieut., Chicago, 1st Medical Squadron, Fort Bliss, Texas.
LERNER, David, 1st Lieut., Chicago, 8th Engineers, Fort McIntosh, Texas.
LERNER, David, 1st Lieut., Au Gres, Mich., 2d Medical Battalion, Fort Sam Houston, Texas.
LOCKLIN, Walter K., 1st Lieut., Ann Arbor, Mich., 2d Medical Battalion, Fort Sam Houston, Texas.
MacDONALD, Hugh, Captain, Skokie, Ill., 2d Medical Laboratory, Fort Sam Houston, Texas.
MATSON, Kenneth L., 1st Lieut., Chicago, 2d Medical Battalion, Fort Sam Houston, Texas.
MENAKER, Gerald J., 1st Lieut., Chicago, Hq. & Hq. Bn., 2d Div., Fort Sam Houston, Texas.
MITCHELL, Mancel T., 1st Lieut., Eau Claire, Wis., 38th Infantry, Fort Sam Houston, Texas.
PAISLEY, Alfred M., 1st Lieut., Jacksonville, Ill., 5th Division, Fort Custer, Mich.
PRUDOWSKY, Harry, 1st Lieut., Milwaukee, 5th Division, Fort Custer, Mich.

REGNIER, Walter O., Captain, Drummond, Wis., 12th Cavalry, Fort Ringgold, Texas.
RIGHTMAN, Bert, 1st Lieut., Chicago, 5th Division, Fort Custer, Mich.
SACHS, Mandel, 1st Lieut., Chicago, 2d Medical Battalion, Fort Sam Houston, Texas.
SALINSKY, Lester V., 1st Lieut., Sheboygan, Wis., 77th Field Artillery, Fort D. A. Russell, Wyo.
SANTORO, Antonio, Captain, Chicago, 7th Cavalry, Fort Bliss, Texas.
SCHWADE, Edward D., 1st Lieut., Shorewood, Wis., Station Hospital, Camp Grant, Ill.
SEIDMON, Edward E. P., 1st Lieut., Chicago, 2d Division Artillery, Fort Sam Houston, Texas.
SHAGAN, Robert M., 1st Lieut., Chicago, 5th Division, Fort Custer, Mich.
SHAPIRO, I. A., 1st Lieut., Detroit, 38th Infantry, Fort Sam Houston, Texas.
SHARP, Mahlon S., 1st Lieut., Detroit, 5th Division, Fort Custer, Mich.
SHULRUFF, Harry I., 1st Lieut., Chicago, Chicago Induction Board, Armory.
SMITH, James J., 1st Lieut., Chicago, 5th Division, Fort Custer, Mich.
SOROCK, Milton L., 1st Lieut., Detroit, 5th Division, Fort Custer, Mich.
STEIN, Albert F., 1st Lieut., Chicago, 5th Division, Fort Custer, Mich.
STERN, Louis S., Captain, West Allis, Wis., 7th Cavalry, Fort Bliss, Texas.
SULLENBERGER, Neil H., 1st Lieut., Detroit, 2d Medical Battalion, Fort Sam Houston, Texas.
TURNBULL, George C., Captain, Evanston, Ill., 82d Field Artillery, Fort Bliss, Texas.
WAGNER, David, Captain, Chicago, 77th Field Artillery, Fort D. A. Russell, Wyo.
WALLACE, John K., II, 1st Lieut., Marion, Ill., 5th Medical Battalion, Fort Custer, Mich.
WALSKE, Benedict R., 1st Lieut., Independence, Wis., Station Hospital, Camp Grant, Ill.
WEAVER, David F., 1st Lieut., Green Bay, Wis., 38th Infantry, Fort Sam Houston, Texas.
YELLEN, Harry J., 1st Lieut., Chicago, 77th Field Artillery, Fort D. A. Russell, Wyo.

SEVENTH CORPS AREA

The following additional medical reserve officers have been ordered to extended active duty by the Commanding General, Seventh Corps Area, up to January 11. The Seventh Corps Area comprises the states of North Dakota, South Dakota, Minnesota, Nebraska, Iowa, Kansas, Missouri, Arkansas and Wyoming.

ALLEN, William Edward, Jr., Captain, St. Louis, Fort Devens, Mass.
BARRY, Gerald Williams, 1st Lieut., Kansas City, Mo., Fort Ord, Presidio of Monterey, Calif.
BJORK, Floyd Joseph, 1st Lieut., Keota, Iowa, Fort Sam Houston, Texas.
BORGMEYER, Henry John, 1st Lieut., Dodge, Neb., Camp Joseph T. Robinson, Ark.
BRANCH, James W., 1st Lieut., Hope, Ark., Fort Knox, Ky.
BREWER, William McKelvey, 1st Lieut., Hays, Kan., Camp Murray, Wash.
BRILLHART, Everett Guy, 1st Lieut., Shelby, Neb., Camp Joseph T. Robinson, Ark.
BROBYN, Thomas Elmer, Captain, Grinnell, Iowa, Fort Ord, Presidio of Monterey, Calif.
BROTT, Clarence Raymond, 1st Lieut., Jansen, Neb., Fort Leonard Wood, Mo.
BROWN, Andrew Porter, 1st Lieut., Salina, Kan., Fort Riley, Kan.
CAMPBELL, James Holmes, 1st Lieut., Joiner, Kan., Fort Ord, Presidio of Monterey, Calif.
CHRISTIANSEN, Harold August, 1st Lieut., Jamestown, N. D., Fort Ord, Presidio of Monterey, Calif.
COLLINS, Leigh George, 1st Lieut., West Point, Neb., Fort Ord, Presidio of Monterey, Calif.
CRAWFORD, William Henry, Major, Omaha, Fort Ord, Presidio of Monterey, Calif.
CUSHING, Robert Louis, 1st Lieut., Fort Scott, Kan., Ford Ord, Presidio of Monterey, Calif.
DECKER, Charles Edward, 1st Lieut., Davenport, Iowa, Camp Murray, Wash.
DEUTCH, Max, Captain, St. Louis, Camp Murray, Wash.
DeYOUNG, George Marion, 1st Lieut., George, Iowa, Camp Murray, Wash.
DILLARD, James Robert, Major, Fargo, N. D., Ford Ord, Presidio of Monterey, Calif.
EATON, Wilbur Smith, 1st Lieut., Plattsmouth, Neb., Fort Crook, Neb.
EDWARDS, Thomas Franklin, Captain, Bismarck, N. D., Fort Ord, Presidio of Monterey, Calif.
ENTRINGER, Albert Joseph, 1st Lieut., Dubuque, Iowa, Camp Murray, Wash.
FELLMAN, Abe C., 1st Lieut., Omaha, Camp Murray, Wash.
GIFFORD, Byron Lee, 1st Lieut., Long Prairie, Minn., Camp Murray, Wash.
GRAUL, Elmer George, 1st Lieut., St. Louis, Camp Murray, Wash.
GRIMES, Henry Burton, Major, Madelia, Minn., Fort Ord, Presidio of Monterey, Calif.
HAMILTON, Benjamin C., Major, Jefferson, Iowa, Camp Murray, Wash.
HELFERTY, John Kenneth, 1st Lieut., Tracy, Minn., Fort Ord, Calif.
JOHNSON, Charles Nelson, Major, Wichita, Kan., Fort Ord, Presidio of Monterey, Calif.
KAMISH, Robert James, 1st Lieut., Halstead, Kan., Ford Ord, Presidio of Monterey, Calif.
McINTIRE, Landon Rolla, Captain, St. Charles, Mo., Fort Lewis, Wash.
MEYER, Jules Owens, 1st Lieut., Grand Rapids, Minn., Fort Ord, Presidio of Monterey, Calif.
OLSSON, Paul Bryant, 1st Lieut., Lexington, Neb., Fort Leavenworth, Kan.
RANSOM, Henry Robert, 1st Lieut., Grand Forks, N. D., Fort Lewis, Wash.
REED, Charles Clay, 1st Lieut., Little Rock, Ark., Jefferson Barracks, Mo.
RYDER, Frank Dell, Major, Grand Island, Neb., Fort Francis E. Warren, Wyo.
SAGI, Joseph Herman, 1st Lieut., Minneapolis, Fort Lewis, Wash.
SEASHORE, Rosel Theodore, 1st Lieut., Duluth, Minn., Fort Ord, Presidio of Monterey, Calif.
SHAW, William John, Major, Fayette, Mo., Camp Murray, Wash.
SMITH, Herman Joseph, 1st Lieut., Des Moines, Iowa, Fort Ord, Presidio of Monterey, Calif.
SNODGRASS, William A., Jr., 1st Lieut., Pine Bluff, Ark., Camp Joseph T. Robinson, Ark.
STEINBERG, Maurice M., 1st Lieut., Omaha, Fort Leavenworth, Kan.
STEWART, Donald Edward, 1st Lieut., Grand Rapids, Minn., Fort Lewis, Wash.
WATSON, Donald Paul, 1st Lieut., Grand Island, Neb., Fort Lewis, Wash.
WILLIAMS, Harold Otis, Captain, Cheney, Kan., Fort Lewis, Wash.
WYATT, Charles Arthur, Major, Holton, Kan., Fort Lewis, Wash.

REGULAR ARMY ORDERS

BOLLERUD, Jack, 1st Lieut., from Brooklyn, to Anchorage, Alaska.
FROITZHEIM, William J., Lieut. Col., from the Hawaiian Department to Fort Niagara, N. Y.
GLAUBMAN, William A., 1st Lieut., from Fort Benning, Ga., and LAWRY, Lee L., 1st Lieut., from Fort George G. Meade, Md., to the Puerto Rican Department.
HEYSINGER, James D., Colonel, Fort Lewis, Wash., retired January 31 for age.
MAYFIELD, George C., Captain, from Hot Springs National Park, Ark., to Hawaiian Department.
WELLS, Francis P., Captain, from Holabird Q. M. Depot, Md., to Panama Canal Department, sailing from New York February 18.
WILLIAMSON, Carl S., Major, and MAUZEY, Armand J., 1st Lieut., from Fort Sheridan, Ill., to Puerto Rican Department.

THE 135th MEDICAL REGIMENT

The 135th Medical Regiment of the Wisconsin National Guard is now assigned as the Third U. S. Army Medical Regiment and is in camp at Camp Shelby, Miss. The following medical officers are on duty with the regiment:

BECKER, Reinhard, Major, Milwaukee.
BECKER, Walter T., Captain, Cedarburg, Wis.
BLECKWENN, William J., Colonel, Madison, Wis.
BOXER, Leo W., Captain, Milwaukee.
CHRISTIANSEN, Wilmer H., Captain, Milwaukee.
EAGLEBURGER, Leon S., Major, Waupun, Wis.
GALLOGLY, John A., 1st Lieut., Milwaukee.
HAUKOHL, Robert S., 1st Lieut., Milwaukee.
HIDDE, Frederick G., Captain, Sheboygan, Wis.
HOLMES, John F., 1st Lieut., Milwaukee.
KENDALL, Earl Thurman, Captain, Milwaukee.
LUDWIG, Erwin P., Captain, Wausau, Wis.
McMAHON, Raymond A., 1st Lieut., Madison, Wis.
MILLER, James E., Captain, Madison, Wis.
MUSSER, Marc J., Jr., Major, Madison, Wis.
PETERSON, John R., 1st Lieut., Milwaukee.
PETERSON, Leo W., Lieut. Colonel, Sun Prairie, Wis.
POHLE, Frederick J., Major, Madison, Wis.
SCHWARZE, Cyril A., 1st Lieut., Watertown, Wis.
THANOS, John N., 1st Lieut., Milwaukee.
VETTER, Edward W., Captain, Stevens Point, Wis.
WEISSMILLER, Lester L., Captain, Madison, Wis.
WILKINSON, Philip M., Captain, Oconomowoc, Wis.

ORGANIZATION SECTION

THE PHYSICIANS FEDERAL INCOME TAX—1941

PREPARED BY THE BUREAU OF LEGAL MEDICINE AND LEGISLATION

Every one who is required to make a federal income tax return must do so on or before March 15, unless an extension of time for filing his return has been granted. For cause shown, the collector of internal revenue for the district in which the taxpayer files his return may grant such an extension, on application filed with him by the taxpayer. This application must state fully the causes for the delay. Failure to make a return may subject the taxpayer to a penalty of 25 per cent of the amount of the tax due.

The normal rate of tax on residents of the United States and on all citizens of the United States regardless of their places of residence is 4 per cent on net income in excess of the exemptions and credits. The Revenue Act of 1940 imposes an additional tax, designated as a defense tax, which in general adds 10 per cent to the amount of tax a person otherwise would be required to pay.

Attention again is called to the provisions of the Public Salary Tax Act of 1939, which subjects to the federal income tax laws the income derived from personal services rendered as an officer or employee of a state, political subdivision, or any agency or instrumentality of either. Theretofore, such income had been considered nontaxable under the federal income tax laws if received for services rendered in carrying out a governmental function. Furthermore, the federal government, under that act, consented to the taxation of states by local taxing authorities of compensation received for personal service as an officer or employee of the United States, any territory or possession or political subdivision, the District of Columbia or any agency or instrumentality of any one or more of the foregoing, if such taxation does not discriminate against such officer or employee because of the source of such compensation. In effect, this act does away with the immunity from federal income taxes theretofore accorded employees of states, their political subdivisions, agencies or instrumentalities and the immunity from state and local taxes of the income received by federal officers or employees.

WHO MUST FILE RETURNS

1. Returns must be filed by every unmarried person and by every married person not living with spouse, if gross income during 1940 was $800 or more.

2. Returns must be filed by every married person who lived with spouse, if gross income during 1940 was $2,000 or over. If both husband and wife had income and their combined gross income was $2,000 or over, they must either file separate returns or, if both are citizens or residents of the United States and if they were living together at the end of the taxable year, they may file a joint return. If a person was married and lived with spouse for only part of 1940, special rules apply with respect to the filing of returns, and physicians who come within this classification should read carefully the instructions given on the tax return blanks.

If the status of a taxpayer, so far as it affects the personal exemption or credit for dependents, changed during the year, the personal exemption and credit must be apportioned, under rules and regulations prescribed by the Commissioner of Internal Revenue with the approval of the Secretary of the Treasury, in accordance with the number of months before and after such change. For the purpose of such apportionment a fractional part of a month should be disregarded unless it amounts to more than half a month, in which case it is to be considered as a month.

As a matter of courtesy only, blanks for returns are sent to taxpayers by the collectors of internal revenue, without request. Failure to receive a blank does not excuse any one from making a return; the taxpayer should obtain the necessary blank from the local collector of internal revenue.

The following discussion covers only matters relating specifically to physicians. Full information concerning questions of general interest may be obtained from the official return blank and from the collectors of internal revenue.

GROSS AND NET INCOMES: WHAT THEY ARE

Gross Income.—A physician's gross income is the total amount of money received by him during the year for professional services, regardless of the time when the services were rendered for which the money was paid, plus such money as he has received as profits from investments and speculation and as compensation and profits from other sources.

Net Income.—Certain professional expenses and the expenses of carrying on any enterprise in which the physician may be engaged for gain may be subtracted as "deductions" from the gross income, to determine the net income on which the tax is to be paid. An "exemption" is allowed, the amount depending on the taxpayer's marital status during the tax year as stated before. These matters are fully covered in the instructions on the tax return blanks.

Earned Income.—In computing the normal tax, but not the surtax, there may be subtracted from net income from all sources an amount equal to 10 per cent of the earned net income, except that the amount so subtracted shall in no case exceed 10 per cent of the net income from all sources. Earned income means professional fees, salaries and wages received as compensation for personal services, as distinguished from receipts from other sources.

The first $3,000 of a physician's net income from all sources may be regarded under the law as earned net income, whether it was or was not in fact earned within the meaning set forth in the preceding paragraph. Net income in excess of $3,000 may not be claimed as earned unless it in fact comes within that category. No physician may claim as earned net income any income in excess of $14,000.

DEDUCTIONS FOR PROFESSIONAL EXPENSES

A physician is entitled to deduct all current expenses necessary in carrying on his practice. The taxpayer should make no claim for the deduction of expenses unless he is prepared to prove the expenditure by competent evidence. So far as practicable, accurate itemized records should be kept of expenses and substantiating

evidence should be carefully preserved. The following statement shows what such deductible expenses are and how they are to be computed:

Office Rent.—Office rent is deductible. If a physician rents an office for professional purposes alone, the entire rent may be deducted. If he rents a building or apartment for use as a residence as well as for office purposes, he may deduct a part of the rental fairly proportionate to the amount of space used for professional purposes. If the physician occasionally sees a patient in such dwelling house or apartment, he may not, however, deduct any part of the rent of such house or apartment as professional expense; to entitle him to such a deduction he must have an office there, with regular office hours. If a physician owns the building in which his office is located, he cannot charge himself with "rent" and deduct the amount so charged.

Office Maintenance.—Expenditures for office maintenance, as for heating, lighting, telephone service and the services of attendants, are deductible.

Supplies.—Payments for supplies for professional use are deductible. Supplies may be fairly described as articles consumed in the using; for instance, dressings, clinical thermometers, drugs and chemicals. Professional journals may be classified as supplies and the subscription price deducted. Amounts currently expended for books, furniture and professional instruments and equipment, "the useful life of which is short," generally less than one year, may be deducted; but if such articles have a more or less permanent value, their purchase price is a capital expenditure and is not deductible.

Equipment.—Equipment comprises property of a more or less permanent nature. It may ultimately wear out, deteriorate or become obsolete, but it is not in the ordinary sense of the word "consumed in the using."

The cost of equipment, such as has been described, for professional use, cannot be deducted as expense in the year acquired. Examples of this class of property are automobiles, office furniture, medical, surgical and laboratory equipment of more or less permanent nature, and instruments and appliances constituting a part of the physician's professional outfit, to be used over a considerable period of time, generally over one year. Books of more or less permanent nature are regarded as equipment and the purchase price is therefore not deductible.

Although the cost of such equipment is not deductible in the year acquired, nevertheless it may be recovered through depreciation reductions taken year by year over its useful life, as described later.

No hard and fast rule can be laid down as to what part of the cost of equipment is deductible each year as depreciation. The amount depends to some extent on the nature of the property and on the extent and character of its use. The length of its useful life should be the primary consideration. The most that can be done is to suggest certain average or normal rates of depreciation for each of several classes of articles and to leave to the taxpayer the modification of the suggested rates as the circumstances of his particular case may dictate. As fair, normal or average rates of depreciation, the following have been suggested: automobiles, 25 per cent a year; ordinary medical libraries, x-ray equipment, physical therapy equipment, electrical sterilizers, surgical instruments and diagnostic apparatus, 10 per cent a year; office furniture, 5 per cent a year.

The principle governing the determination of all rates of depreciation is that the total amount claimed by the taxpayer as depreciation during the life of the article, plus the salvage value of the article at the end of its useful life, shall not be greater than its purchase price or, if purchased before March 1913, either its fair market value as of that date or its original cost, whichever may be greater. The physician must in good faith use his best judgment and claim only such allowance for depreciation as the facts justify. The estimate of useful life, on which the rate of depreciation is based, should be carefully considered in his individual case.

In a Treasury Decision, approved Feb. 28, 1934, No. 4422, it was held, among other things, that:

1. The cost to be recovered shall be charged off over the useful life of the property.

2. The reasonableness of any claim for depreciation shall be determined on the conditions known to exist at the end of the period for which the return was made.

3. Where the cost or other basis of the property has been recovered through depreciation or other allowances, no further deduction for depreciation shall be allowed.

4. The burden of proof will rest on the taxpayer to sustain the deduction claimed.

5. The deduction for depreciation in respect to any depreciable property for any taxable year shall be limited to such ratable amount as may reasonably be considered necessary to recover during the remaining life of the property the unrecovered cost or other basis.

Particular attention is called to the last of the foregoing provisions. If, in prior years, rates have been claimed which, if continued, will fully depreciate the cost, less salvage, before the end of its useful life, based on conditions now known, a reestimate of the remaining useful life should now be made and the portion of the cost that had not been depreciated at the beginning of the year 1940 (for a return for the year 1940) should be spread over this reestimated life.

Medical Dues.—Dues paid to societies of a strictly professional character are deductible. Dues paid to social organizations, even though their membership is limited to physicians, are personal expenses and not deductible.

Postgraduate Study.—The Commissioner of Internal Revenue holds that the expense of postgraduate study is not deductible.

Traveling Expenses.—Traveling expenses, including amounts paid for transportation, meals and lodging, necessarily incurred in professional visits to patients and in attending medical meetings for a professional purpose, are deductible.

Automobiles.—Payment for an automobile is a payment for permanent equipment and is not deductible. The cost of operation and repair, and loss through depreciation, are deductible. The cost of operation and repair includes the cost of gasoline, oil, tires, insurance, repairs, garage rental (when the garage is not owned by the physician), chauffeurs' wages, and the like.

Deductible loss through depreciation of an automobile is the actual diminution in value resulting from obsolescence and use and from accidental injury against which the physician is not insured. If depreciation is computed on the basis of the average loss during a series of years, the series must extend over the entire estimated life of the car, not merely over the period in which the car is possessed by the present taxpayer.

If an automobile is used for professional and also for personal purposes—as when used by the physician partly for recreation, or so used by his family—only so much of the expense as arises out of the use for professional purposes may be deducted. A physician doing an exclusive office practice and using his car merely to go to and from his office cannot deduct depreciation or operating expenses; he is regarded as using his car for his personal convenience and not as a means of gaining a livelihood. What has been said in respect to automobiles applies with equal force to horses and vehicles and the equipment incident to their use.

MISCELLANEOUS

Contributions to Charitable Organizations. — For detailed information with respect to the deductibility of charitable contributions generally, physicians should consult the official return blank or obtain information from the collectors of internal revenue or from other reliable sources. A physician may not, however, deduct as a charitable contribution the value of services rendered an organization operated for charitable purposes.

Social Security Taxes.—The excise taxes imposed on employers by section 804, title VIII, and section 901, title IX, of the Social Security Act, commonly referred to as old age and unemployment benefit taxes, are deductible annually by employers in computing net income for federal income tax purposes. If the taxpayer's return is made on a cash basis, as are the returns of practically all physicians, the taxes are deductible for the year in which they are actually paid. If the return is made on an accrual basis, the taxes are deductible for the year in which they accrue, irrespective of when they are actually paid. Employees, including physicians whose employment brings them within that category, may not deduct the tax imposed on them by section 801, title VIII, of the Social Security Act, generally referred to as the old age benefits tax. If, however, the employer assumes payment of the employee's tax and does not withhold the amount of the tax from the employee's wages, the amount of the tax so assumed may be deducted by the employer, not as a tax paid but as an ordinary business expense.

Laboratory Expenses. — The deductibility of the expenses of establishing and maintaining laboratories is determined by the same principles that determine the deductibility of corresponding professional expenses. Laboratory rental and the expenses of laboratory equipment and supplies and of laboratory assistants are deductible when under corresponding circumstances they would be deductible if they related to a physician's office.

Losses by Fire or Other Causes.—Loss of and damage to a physician's equipment by fire, theft or other cause, not compensated by insurance or otherwise recoverable, may be computed as a business expense and is deductible, provided evidence of such loss or damage can be produced. Such loss or damage is deductible, however, only to the extent to which it has not been made good by repair and the cost of repair claimed as a deduction.

Insurance Premiums.—Premiums paid for insurance against professional losses are deductible. This includes insurance against damages for alleged malpractice, against liability for injuries by a physician's automobile while in use for professional purposes, and against loss from theft of professional equipment and damage to or loss of professional equipment by fire or otherwise. Under professional equipment is to be included any automobile belonging to the physician and used for strictly professional purposes.

Expense in Defending Malpractice Suits.—Expense incurred in the defense of a suit for malpractice is deductible as a business expense.

Sale of Spectacles.—Oculists who furnish spectacles, etc., may charge as income money received from such sales and deduct as an expense the cost of the article sold. Entries on the physician's account books should in such cases show charges for services separate and apart from charges for spectacles, etc.

MEDICAL LEGISLATION

MEDICAL BILLS IN CONGRESS

Change in Status.—H. R. 2112 has been reported to the House with recommendation that it pass, proposing to authorize the Secretary of the Navy to appoint in time of war or national emergency declared by the President to exist, for temporary service, such acting assistant surgeons as the exigencies of the service may require. Under existing law not more than one hundred may be appointed for temporary service.

Bills Introduced.—S. 479, introduced by Senator Barbour, New Jersey, proposes that no employer having contractual relations with the United States and engaged in the manufacture for or sale to the United States of supplies or equipment of any description shall discriminate against any applicant for employment suffering from a physical disability, if the applicant has successfully completed a course of vocational training financed or directed in whole or in part by any agency of the United States government and if the applicant has been certified as qualified to perform the work for which he has made application. S. 617, introduced by Senator McNary, Oregon, proposes service pensions for all persons who served ninety days, in foreign service, under the jurisdiction of the Quartermaster General, Surgeon General, of the United States Army, the Secretary of the Navy, or Marine Corps, during the Spanish-American War, including the Philippine Insurrection and the Chinese Boxer Rebellion. S. 667, introduced by Senator Walsh, Massachusetts, proposes to authorize the Administrator of Veterans' Affairs to furnish domiciliary and hospital care and medical treatment to World War veterans of the United States merchant marine. S. 670, introduced by Senator Walsh, Massachusetts, proposes to extend the federal old age and survivors' insurance benefits of the Social Security Act to certain employees of religious, charitable, scientific, literary or educational organizations. H. J. Res. 99, introduced by Representative Coffee, Washington, will, if enacted, authorize the Surgeon General of the United States Public Health Service to conduct an investigation and survey of the conditions in the United States existing now and during the past twenty-five years with respect to the importation, production, distribution and use of narcotics. H. R. 2679, introduced by Representative Pearson, Tennessee, proposes free hospitalization and medical attention for all veterans of the World War and the Spanish-American War in government facilities. H. R. 2818, introduced by Representative Knutson, Minnesota, proposes to add a new title to the Social Security Act whereunder grants will be made to states for aid to the physically handicapped.

DISTRICT OF COLUMBIA

Bill Introduced.—H. R. 1875, introduced by Representative Boland, Pennsylvania, proposes to direct the Commission on Licensure to Practice the Healing Art to issue a license to practice the healing art in the District of Columbia to Dr. Peter Florey.

STATE MEDICAL LEGISLATION

Massachusetts

Bills Introduced.—S. 560, to supplement the medical practice act, proposes, in effect, to nullify the requirement of law that an applicant for a license to practice medicine, among other things, must show attendance and graduation from a medical school approved by the approving authority. The bill proposes that any person who (1) has completed a two year premedical collegiate course, or its equivalent, (2) has completed four years of thirty-two weeks in each year in a medical school, or medical schools, incorporated under the laws of Massachusetts which have the power to confer medical degrees and has received the degree of doctor of medicine from such school, and (3) has served a year as an intern or its equivalent in a hospital must be examined by the board of registration in medicine. H. 609 proposes that after the removal of any limb or organ the operating physician must deliver a written statement of explanation to the patient or to his representative explaining the nature of the operation performed and giving his reasons for considering such an operation necessary. H. 610 proposes after the removal of any organ or limb the physician shall explain to the patient or his or her representatives that it is their right to view the part removed from the body alone or in the presence of any physician they may choose and that they may have a full explanation alone, or in the presence of any physician they may choose, as to the necessity of such removal. The bill further proposes that after the completion of such an operation some physician, other than the operating physician, to be designated by the person in charge of the hospital where the operation was performed, shall take charge of the limb or organ and seal in a preservative and lock it away. The limb or organ so preserved is not to be tampered with until it is known whether the patient or the patient's representative wish to view it, provided that the limb or organ need not be kept and preserved for more than six weeks after the operation. H. 868 proposes to prohibit the operation of a convalescent home or a nursing home unless licensed. A convalescent or nursing home is defined as a home in which three or more persons recovering from an illness and not members of the immediate family of the owner or operator are, for hire, gain or reward, provided with convalescent or nursing care. H. 872 proposes to enact what it refers to as the Uniform State Food, Drug and Cosmetic Act to regulate the manufacture, sale, distribution and advertising of foods, drugs, cosmetics and therapeutic devices. H. 902 proposes to enact a new practice act for the licensing of registered nurses and registered attendants. Apparently the bill, if enacted, would not limit the practice of nursing only to registered nurses or registered attendants but would prohibit a person from practicing as a registered nurse or as a registered attendant only unless she was so licensed. H. 907 proposes to create a department of industrial accidents to consist of the industrial accident board and a medical commission, proposed by the bill. The bill proposes that the industrial accident board shall refer questions regarding medical treatment, rehabilitation of injured employees and industrial disease to the medical commission, which is to have powers to make inquiry, investigations and examinations. Reports of the medical commission as to the medical aspects of issues involved are to be transmitted to the industrial accident board, which must follow the recommendations in making decisions as to the merits of the case. H. 1121, to supplement the unemployment compensation act, proposes that any person absent from work on account of sickness shall not be therefore debarred from receiving unemployment compensation benefits. H. 1229 apparently is designed to supplement the medical practice act, but what it proposes is not clear. The bill states "That any graduate of a medical school in whose state it is situated in, and the board of examination of that state does not allow these graduates to take the examination in that state that graduates of a school of this standing be not permitted to take the examinations in Massachusetts." The bill further proposes that graduates of a foreign medical school be not permitted to be examined in Massachusetts until they have established a legal residence in the state and until they have been residents for at least five years. H. 1234 proposes "That all couples, applying for a marriage license, shall present to the registrar of marriages a certificate from a physician or clinic regularly licensed by the state of Massachusetts to practice medicine, stating that a physical examination and a serological complement fixation or flocculation test was made at a regularly approved laboratory, registered under the laws of the commonwealth." The bill further proposes that "when the blood test is positive for syphilis in one or both the parties applying for marriage, the physician is held on his honor, and he must insist and see that treatment is instituted at once, and that a faithful promise is made to carry out the treatment until discharged by the doctor or the clinic." H. 2035 is an initiative petition to provide that the law prohibiting the distribution of contraceptive drugs and materials or the giving of contraceptive advice "shall not apply to treatment or prescription given to married persons for protection of life or health by or under the direction" of licensed physicians nor to teaching in chartered medical schools; nor to publication or sale of medical treatises or journals. H. 1922, to amend the medical practice act, proposes apparently to require all applicants for licenses to practice medicine to be citizens of the United States.

New York

Bills Introduced.—S. 313 and A. 371 propose to establish a system of compulsory health insurance, the benefits of which are to consist of all kinds of medical, dental and hospital services and cash and maternity benefits. All employees are embraced in the compulsory features of the bill except employees (1) engaged in agricultural labor, (2) engaged in domestic service for an employer having less than three employees engaged in such service, (3) employed at nonmanual work and receiving wages in excess of $30 a week or (4) employed under an express contract for a term of not less than one year at total wages for a year in excess of $1,500. This system, the bills propose, is to be financed by a series of payroll taxes levied on employer and on employee and by state contributions. A. 62 proposes to enact a separate chiropractic practice act and to create an independent board of chiropractic examiners to examine and license applicants for licenses to practice chiropractic. The bill proposes to define chiropractic as "the science of locating and the removing of nerve interference in the human body, where such interference is the result of or caused by misalignment or subluxations of the vertebral column. It excludes operative surgery, the reduction of fractures, the prescription or use of drugs or medicine, and the practice of obstetrics." A. 364 proposes to prohibit a person having a communicable or contagious disease transmittible [sic] through food or who is suffering from any condition which may cause contamination of food from doing any work involving the handling of food in any place where food is manufactured, prepared, sold or served. A. 370 proposes to require every local board of health and every health officer to exercise proper and vigilant medical inspection of all persons, 21 years of age or over, infected with poliomyelitis and to provide at the remedial states of the disease suitable surgical, medical or therapeutic treatment or hospital care, and necessary appliances and devices for such persons so infected or exposed who cannot otherwise be provided for. One half of the cost of providing such care and appliances is to be made a charge against the county, and the other one half of the cost is to be paid by the state.

Tennessee

Bills Introduced.—H. 225, to enact a separate naturopathic practice act and to create a board of naturopathic examiners to examine and license applicants for licenses to practice naturopathy, was reported unfavorably to the House January 22. The bill proposes to define naturopathy as "the system of the healing art, study, and science, which uses and prescribes the following practices and usages: diagnosis and the practice of the combined psychological, physiological, mechanical, and material sciences of healing to aid in purifying, cleansing, and normalizing human tissues for the preservation and restoration of health, as taught in schools, institutes, and colleges of Naturopathy, which shall include, among other agencies: physio-therapy, hydro-therapy, mechano-therapy, phyto-therapy, electrotherapy,

psychotherapy, chromotherapy, zone-therapy, helio-therapy, corrective and orthopedic gymnastics, external applications, manipulation, nutritional control, psychology, biochemistry, hygiene, first aid, sanitation, dietetics, mechanical and electrical appliances, herbology, massage, anatomical correction; x-ray for diagnostic purposes only, irrigations of the body orifices; and that Naturopathy and Naturopathy shall be constructed as synonymous terms. And that also Sanipractic and Drugless Physicians shall be interpreted as the same as Naturopathy and its practice, and shall hereby be governed and regulated by this Act and Chapter. Provided, however, that nothing in this chapter shall be construed or held to authorize any Naturopathic Physician licensed hereunder to use narcotic drugs or practice surgery, or Chiropody." S. 240 and H. 334 propose to appropriate $210,000 for each of the fiscal years 1941-42 and 1942-43 to organize, operate and maintain local full time health services throughout the state, these amounts to be used for the specific purpose of matching on a dollar for dollar basis federal funds that are available to the Tennessee Department of Public Health through provisions of the Federal Social Security Act and other federal appropriations for public health purposes. The bills also propose to appropriate for each fiscal year noted $50,000 to be used to provide essential and additional public health services in areas where special financial or public health problems exist, for the establishment of approved local public health services where such services do not exist as of the date either of these bills is enacted and for any other emergency or necessary public health service for which financial provisions have not been made. H. 352 and S. 277 propose to appropriate for the coming fiscal year $175,000 to be allocated at the rate of not less than $2,500 per annum to each county and to each of the four major city governments maintaining an approved cooperative full-time public health service to be used for the specific purpose of matching on a dollar-for-dollar basis federal or other funds that are available to the Tennessee Department of Public Health through provisions of the Federal Social Security Act and other federal or other appropriations for public health purposes. For the fiscal year beginning July 1, 1942, the amount to be appropriated is to be $190,000. The bill also proposes to appropriate an additional $50,000 for the next two ensuing fiscal years to be used for the purpose of providing essential public health services in areas where special financial or public health problems exist, for the establishment of approved local public health services where such services do not exist and for any other emergency or essential public health service required for the protection of the public health. H. 351 and S. 278 propose to authorize the Division of Tuberculosis Control, in making provisions for the medical and surgical care of emergency and meritorious cases among economically dependent persons, to expend an amount not to exceed 10 per cent of the total funds available for hospitalization at a rate not to exceed $2.50 per patient per diem without an equal matching requirement from counties or municipalities. H. 425 and S. 315, to amend the medical practice act, propose (1) to eliminate that provision in the present law that requires four members of the medical examining board to be nonsectarian physicians, one member to be a homeopath and one member to be an eclectic, and (2) to set the fee for the issuance of a license by reciprocity at $50.

Utah

Bills Introduced.—S. 43, to amend the chiropody practice act, proposes that an applicant for a license to practice chiropody must either (1) have completed two years in a recognized college of liberal arts, and must be a graduate of a regularly established school of chiropody as recognized by the National Association of Chiropodists, which requires as a prerequisite to graduation the completion of three chiropodical-podiatric terms of at least three thousand, one hundred and twenty hours of class work given over a period of not less than three different calendar years; or (2) have completed one year in a recognized college of liberal arts or of the sciences and have graduated from a regularly established school of chiropody as recognized by the National Association of Chiropodists, which requires as a prerequisite to graduation the completion of four chiropodical-podiatric terms of at least four thousand, one hundred and sixty hours of class work given over a period of not less than four different calendar years. S. 12, to supplement the laws relating to the practice of the healing arts, proposes to authorize the issuance of the following additional classes of licenses to practice the healing arts: (1) "To practice as a naturopathic physician without the use of drugs and without operative surgery in accordance with the tenets of a professional school of naturopathy recognized by the department of registration" and (2) "To practice as a naturopathic physician and surgeon in accordance with the tenets of a professional school of naturopathy recognized by the department of registration, and having had class work equal to the standard of other practitioners of surgery." S. 13, to amend the law relating to the practice of dentistry, proposes to authorize the revocation or suspension of a licentiate: (1) "Advertising his dental business or treatment or devices by untruthful, improbable or impossible statements, or advertising in any manner except by the use of newspapers, periodicals, signs, cards, radio and other lawful means of advertising, provided, that definite fixed prices or charges to be made be advertised in the manner and by the means hereinabove specified, and provided further that advertising in any manner or by any means whatsoever as in this act provided, shall be only in the name of the licensed dentist," and (2) "Failing to keep his price list of all dental operations of both minimum and maximum prices in a conspicuous place in his reception room, and at each dental chair in his dental office; The price list shall be in letters not smaller than one inch in size, and if the dentist employs a commercial dental laboratory to do his prosthetic work, price list of said laboratory shall be attached thereto." S. 59 proposes to transfer the enforcement of the uniform narcotic drug act and of the prophylactic act from the Department of Registration to the Board of Pharmacy. S. 67 proposes to enact a so-called occupational disease disability compensation act and to authorize the recovery of compensation by any employee who sustains from his employment one or more of the twenty-seven occupational diseases enumerated in the bill. S. 93, to amend the sales tax law, proposes to levy a tax of 2 per cent on the amount paid to any person for professional services rendered. S. 102 proposes to enact what it cites as the Food, Drug and Cosmetic Act to regulate the manufacture, sale, distribution or advertising of foods, drugs, cosmetics and therapeutic devices.

OFFICIAL NOTES

Hotels in Cleveland

On advertising page 46 of this issue of THE JOURNAL may be found a table containing a list of hotels in Cleveland and rates for rooms.

The form printed in the advertising pages may be clipped and, when it has been properly filled in, should be sent at once to Dr. Edward F. Kieger, Chairman, Subcommittee on Hotels of the Local Committee on Arrangements, Cleveland Convention and Visitors' Bureau, Incorporated, 1604 Terminal Tower, Cleveland, Ohio.

RADIO BROADCASTS

The next three programs to be broadcast in the series Doctors at Work are as follows:

February 12. Medical Detective.
February 19. One Man's Poison.
February 26. Exploring Man's Mind.

The program is scheduled over the Blue network of the National Broadcasting Company Wednesdays at 10:30 p. m. eastern standard time (9:30 central, 8:30 mountain, 7:30 Pacific time).

Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

CALIFORNIA

Personal.—Dr. Julius A. Katzive, assistant director of the Mount Sinai Hospital of New York for several years, has been appointed superintendent of the Mount Zion Hospital of San Francisco.

Hospital Conference.—Dr. Cyrus C. Sturgis, professor of internal medicine, University of Michigan Medical School, Ann Arbor, was the guest speaker of the San Jose Hospital Association at its conference January 6-10. Dr. Sturgis's subjects were the nature and treatment of hypertension, the hemorrhagic diseases, the menace and treatment of obesity, the macrocytic anemias and the anemias of pregnancy, and the therapeutic value of blood transfusions, preserved blood and blood substitutes.

Society News.—The Alameda County Medical Association was addressed January 20 by William H. Hollander, Oakland attorney, on "The Fifth Column Menace in America." Drs. Lloyd F. Hawkinson, Oakland, and Adelbert M. Moody, San Francisco, presented a symposium on basal metabolism.——The Los Angeles Society of Neurology and Psychiatry was addressed, January 15, by Drs. Hans V. Briesen on "Neurosurgical Consideration of Spinal Canal Impingement by Hypertrophied Ligamenta Flava and Protruded Intervertebral Disks" and George Mosser Taylor, "Clinical Experience with the Sciatic Syndrome."

COLORADO

The Sewall Lectures.—Dr. Cyrus C. Sturgis, professor of internal medicine, University of Michigan Medical School, Ann Arbor, will deliver the Henry Sewall Memorial Lectures at the University of Colorado School of Medicine, Denver. His subject on February 11 will be "The Therapeutic Value of Blood and Blood Substitutes" and on February 13 "The Hemorrhagic Diseases."

CONNECTICUT

Waterbury Forms a Health Council.—A health council comprising representatives of medical, dental, civic and other agencies has been formed in Waterbury. The purpose of the council, which is an outgrowth of the Waterbury Citizens' Advisory Committee on Health, will be, among other things, to develop a cooperative program with all community public health agencies. The establishment of the council was urged in a recommendation following a public health survey made in 1939 by Ira V. Hiscock, C.P.H., and associates of the department of public health of Yale University School of Medicine, New Haven.

DISTRICT OF COLUMBIA

Society News.—The Washington Urological Society will be addressed by Dr. Stanford W. Mulholland, Philadelphia, February 19, on "Hypertension with Unilateral Renal Disease."——The Medical Society of the District of Columbia will be addressed, February 26, by Drs. Arthur M. Grossman on "Practical Therapy with Vitamin K"; Norman H. Jolliffe, New York, "Newer Knowledge of the Vitamin B Complex," and H. Trendley Dean, D.D.S., "Some Recent Findings with Respect to Dental Caries."

New Health Center.—The new Southwest Health Center was opened for inspection by the District health department on December 18. The three story building, which cost $200,000, contains a laboratory and maternal and child welfare, social, chest and dental clinics. Dr. Charles B. Campbell, Washington, chairman of the health committee of the Federation of Citizens' Associations, delivered the invocation. Dr. George C. Ruhland, Washington, District health officer, was presented with a certificate of merit by the Southwest Citizens' Association.

IDAHO

Hospital News.—The new Gritman Memorial Hospital was opened at Moscow recently at a cost of $105,000. The three story building was financed by contributions from local citizens as a memorial to the late Dr. Charles L. Gritman.——Two floors have been added to the original wing of St. Joseph's Hospital, Lewiston.——Lakeside Hospital, Coeur d'Alene, has recently increased its capacity from fifteen to thirty-five beds.

ILLINOIS

Personal.—Lieut. Marcus D. Burnstine, Columbus, Ohio, medical reserve officer, has been named physician in charge of the health service station for civilian employees at the Rock Island Arsenal, succeeding Dr. Roderick G. St. Pierre, Rock Island, who went to Portland, Ore.

Resident in Otolaryngology.—The position of junior resident in otolaryngology has become vacant at the Illinois Charitable Eye and Ear Infirmary. Applications should be addressed to Dr. Joseph C. Beck, assistant dean of instruction at the infirmary, 904 West Adams Street, Chicago.

Hospital News.—The Clara A. Abbott trust has given $40,000 to the Evanston Hospital, supplementing an earlier donation of $250,000. The money is being used for construction of the Abbott Memorial Building at the hospital, which will house clinical and research laboratories, an auditorium for medical teaching and facilities for outpatient diagnostic tests. Mrs. Abbott was the widow of Dr. Wallace C. Abbott, founder of the Abbott Laboratories.

Chicago

Annual Meeting of Heart Association.—Lieut. Col. Charles G. Hutter, Medical Corps, U. S. Army, liaison officer of the Office of the Surgeon General to the American Medical Association, will be the principal speaker and guest of honor at the annual session of the Chicago Heart Association in Abbott Hall February 12. Colonel Hutter's subject will be "Heart Disease and National Defense."

South Side Medical Assembly.—The midwinter meeting of the South Side Medical Assembly will be held on February 19 with clinics in the morning at various hospitals and afternoon and evening sessions at the Shoreland Hotel. Symposiums will make up the afternoon program, and after dinner Dr. James R. Bloss, Huntington, W. Va., will speak on "Sterility Studies in the Female." The assembly is an organization consisting of all the south side branches of the Chicago Medical Society.

Dr. Joseph Brennemann Retires.—After serving three years beyond the retirement age, Dr. Joseph Brennemann resigned, January 1, as chief of staff of the Children's Memorial Hospital, a position he had occupied since 1921. He has been succeeded by Dr. Charles Anderson Aldrich, a member of the staff for twenty years. Born in Peru, Ill., in 1872, Dr. Brennemann graduated at Northwestern University Medical School in 1900. He has been professor of pediatrics at the University of Chicago, the School of Medicine, since 1921.

INDIANA

Medical History.—Plans are under way to compile a history of medicine in Indiana. Members of the profession are urged to send in suggestions or any material they may have available to Miss Ruth McNutt, librarian, Indiana University School of Medicine, Medical Center, 1040 West Michigan Street, Indianapolis. Miss McNutt will file the material for later use by the Indiana Association for the History of Medicine.

Dr. Shanklin Honored.—Dr. Eldridge M. Shanklin, Hammond, for twenty-five years secretary of the Lake County Medical Society, was voted honorary membership in the society "for long and distinguished service" at a meeting, January 10. This is the first time in forty-three years that the society has conferred such an honor. Dr. Shanklin ended his twenty-fifth year as secretary of the society in 1938. He was president in 1920. He also served as president of the Indiana State Medical Association in 1925. Dr. Shanklin graduated at the Medical College of Indiana, Indianapolis, in 1902. Among other offices, he has been a member of the state board of registration in medicine, serving for three years as executive officer. He has been editor of the state medical journal for nine years. Formal presentation of the honorary membership will be made on February 13.

MICHIGAN

Personal.—Dr. Martha L. Longstreet was chosen as Saginaw's "outstanding citizen for 1940" recently when she was awarded an honorary life membership in the Saginaw Chamber of Commerce.——Mr. George E. Phillips, superintendent of Herman Kiefer Hospital, Detroit, for twenty-six years, died

recently.——Dr. Lloyd F. Catron, assistant professor of pathology, University of Michigan Medical School, Ann Arbor, resigned, December 31, to become pathologist and director of laboratories in the Akron (Ohio) City Hospital. Dr. Catron graduated at Rush Medical College, Chicago, in 1932.

County Society Sponsors Public Exhibit.—The Kent County Medical Society opened a health exhibit in the Grand Rapids Public Museum, January 9. The exhibit will continue for six months, the themes to be changed from time to time, covering tuberculosis, pneumonia, cancer, infantile paralysis, allergy and diabetes. The auxiliary to the county medical society is planning a display of antique medical instruments, the city health department one on public health work, and the Kent County Dental Society one on dentistry. The Women's Field Army of the American Society for the Control of Cancer is cooperating in the exhibits on cancer. Grand Rapids Junior College is lending a series of charts on anatomy to be used in connection with the exhibits. Dr. William R. Vis, Grand Rapids, is chairman of the committee in charge of the exhibit.

Annual Clinic Day.—The Mount Carmel Mercy Hospital, Detroit, conducted its annual clinic day January 29. The following program was to be presented:

Dr. Grover C. Penberthy, Detroit, Surgical Treatment of Acute Osteomyelitis Combined with the Use of Sulfonamide Compounds.
Dr. Frederick A. Coller, Ann Arbor, The Closure and Healing of Wounds.
Dr. Charles H. Slocumb, Rochester, Minn., Differential Diagnosis and Treatment of the Arthritides.
Dr. Edgar H. Norris, Detroit, New Detroit Medical Center.
Dr. George Crile Jr., Cleveland, Hyperthyroidism.
Dr. Russell L. Haden, Cleveland, Treatment of Pernicious Anemia.
Dr. Morris Edward Davis, Chicago, Uses and Abuses of Cesarean Section.

At a dinner in the evening at the Hotel Statler, Dr. Edmund D. Margrave, Royal Oak, chief of staff of the hospital, was toastmaster. The speakers included Dr. Allan W. McDonald, Detroit, president, Wayne County Medical Society; the Hon. Murray D. Van Wagoner, governor of Michigan; the Hon. George Dondero, U. S. Congressman from Michigan, and the Hon. Martin Dies, U. S. Congressman from Texas.

MINNESOTA

Dr. Beadie Retires.—Dr. William D. Beadie, who has been active in tuberculosis work in Minnesota for almost twenty-five years, retired January 1 as superintendent of Mineral Springs Sanatorium, Cannon Falls, a position he had held for the past seventeen years. A graduate of McGill University Faculty of Medicine, Montreal, Dr. Beadie practiced medicine in southern Minnesota and in St. Paul, became medical director of Pokegama Sanatorium in 1917 and of Mineral Springs in 1923. Dr. Karl H. Pfuetze, formerly of Nopeming, has been named to succeed Dr. Beadie at Mineral Springs.

NEW JERSEY

New York University Courses in Newark.—New York University College of Medicine is presenting a course in amputations at the City Hospital, Newark, Saturday mornings from March 1 to April 12. Dr. Henry H. Kessler, Newark, will be director of the course, which will be given for not less than six nor more than eighteen physicians. Applications should be sent to the Office of the Dean, New York University College of Medicine, 477 First Avenue, New York, before February 22. A course of lectures on diseases of the liver and biliary tract will be given at the Newark City Hospital under the direction of Dr. Manfred Kraemer Tuesday and Thursday mornings from February 25 through March 27. Applications for this course must be received by February 18. The class will be limited to twelve.

Society Ex-Presidents Back Aid to Britain.—All the living ex-presidents of the Medical Society of New Jersey issued a joint statement, January 22, pledging their support to the President of the United States in behalf of total defense and in his effort to give all material aid to Great Britain short of war, irrespective of cost. The statement further called on the representatives from New Jersey in Congress to lend their support to a program to give the fullest aid to Great Britain and her allies. It was signed by Drs. Edward J. Ill, Wells P. Eagleton, Francis R. Haussling and Edward M. Zeh Hawkes, Newark; Walt P. Conaway and William J. Carrington, Atlantic City; Lucius F. Donohue, Bayonne; Andrew F. McBride, Paterson; George N. J. Sommer, Trenton; Frederick J. Quigley, Union City; Lancelot Ely, Somerville; Marcus W. Newcomb, Browns Mills; Spencer T. Snedecor, Hackensack, and William G. Herrman, Asbury Park.

NEW YORK

Lectures for Practitioners.—The council committee on public health and education of the Medical Society of the State of New York arranged a "Teaching Day" for the Wyoming County Medical Society in Castile, January 8. The speakers were Drs. Francis J. Gustina, Buffalo, on "The Use of Biologicals in the Diagnosis and Treatment of Communicable Diseases, with Discussion of Technics and Results" and Ward L. Ekas, Rochester, on "The Hemorrhagic States of Pregnancy, Placenta Praevia and Other Conditions." Three lectures on pediatrics are being presented before the Chemung County Medical Society in Elmira. Dr. Charles Hendee Smith, New York, gave the first, January 8, on "Pneumonias of Childhood"; Dr. Katharine G. Dodge, New York, will speak February 12 on "Rheumatic Fever, Chorea and Heart Disease," and Dr. Gaylord W. Graves, New York, March 12 on "Preventive Pediatrics and the Periodic Health Examination."

Aviation Award Presented to Dr. Bauer.—The first John Jeffries Award in aviation medicine was presented to Dr. Louis H. Bauer, Hempstead, L. I., by the Institute of the Aeronautical Sciences in New York, January 28. John Jeffries was a physician, born in Boston in 1744, who graduated from Harvard and later practiced in London. In 1784 he made a flight from London with Blanchard, a French balloonist, during which he recorded temperature, humidity, electrical charges and density of the air. The next year Jeffries and Blanchard made the first crossing of the English Channel by air. The institute will present the award annually for contributions to the advancement of aeronautics through medical research. Dr. Bauer graduated from Harvard Medical School, Boston, in 1912 and entered the Medical Corps, U. S. Army, in 1913. He was the first commandant of the School of Aviation Medicine of the Army Air Corps; also the first medical director of the aeronautics branch of the U. S. Department of Commerce, serving from 1926 to 1930, in which year he resigned from the army. He organized and was the first president of the Aero Medical Association and is editor of the *Journal of Aviation Medicine* and consultant in aviation medicine and cardiology to the Civil Aeronautics Authority. He is attending cardiologist to the Nassau Hospital, Mineola, and to the Meadowbrook Hospital, Hempstead.

New York City

Fifth Harvey Lecture.—Howard B. Lewis, Ph.D., professor of biological chemistry and chairman of the department, University of Michigan Medical School, Ann Arbor, will deliver the fifth Harvey Lecture of the current series at the New York Academy of Medicine, February 20, on "The Significance of the Sulfur-Containing Amino Acids in Metabolism."

Symposium on Wheezing.—The Tuberculosis Sanatorium Conference of Metropolitan New York will hold a clinical session on chronic pulmonary disease February 19 at which a symposium on "Clinical Aspects of Wheezing" will be presented. The speakers will be Drs. Robert A. Cooke, from the standpoint of the allergist; Mervin C. Myerson, the bronchoscopist, and Paul Klemperer, the pathologist.

Symposium on Vitamins.—Long Island College of Medicine, Brooklyn, presented a symposium at an all day meeting January 23 with the following speakers discussing avitaminosis in relation to the subjects given: Drs. Thomas T. Mackie, medicine and surgery; Arthur W. Grace, dermatology; Benjamin Kramer, Brooklyn, pediatrics; H. Russell Meyers, Brooklyn, nervous diseases; Alfred C. Beck, Brooklyn, obstetrics, and C. Raymond Wells, D.D.S., Brooklyn, oral conditions.

The Physician in National Defense.—The metropolitan New York chapter of the Association of Military Surgeons of the United States held a symposium on "The Mission of the Physician in National Defense," January 23, at the New York Academy of Medicine. The speakers were:

Dr. Claude C. Pierce, The Medical Officer in the U. S. Public Health Service.
Col. Howard W. Barker, The Medical Officer in the Veterans Administration.
Capt. Edward C. White, The Medical Officer in the U. S. Navy.
Col. Charles M. Walson, The Medical Officer in the U. S. Army.
Dr. Charles F. W. Bove, The Civilian Physician and National Defense.

Dr. Van Etten Honored.—The Bronx Medical Association gave a dinner December 7 in honor of Dr. Nathan B. Van Etten, President of the American Medical Association, celebrating his fiftieth year in the practice of medicine. More than one hundred and fifty attended. The group, of which Dr. Van Etten is a charter member, presented to him a watch inscribed "To Dr. Nathan B. Van Etten, President of the

American Medical Association, 1940; for fifty years zealous exponent of medical ideals and ethics, with high regard, from the Bronx Medical Association."

Lilly Award to Dr. Woolley.—Dilworth Wayne Woolley, Ph.D., fellow on the staff of the Rockefeller Institute for Medical Research, won the $1,000 Lilly award and a bronze medal given at the annual convention of the Society of American Bacteriologists in St. Louis in December. The award, established by Eli Lilly and Company, is presented annually to a man or woman under 31 years of age who has made exceptional contributions to knowledge of bacteriology or immunology in a noncommercial or educational institution. Dr. Woolley was honored for his research on the hemolytic streptococcus. He graduated from the University of Alberta in 1935.

PENNSYLVANIA

Society News.—Dr. Thomas St. Clair, Latrobe, among others, addressed the Westmoreland County Medical Society, Greensburg, January 21, on "Analgesia in Obstetrics."——Dr. Jacques P. Guequierre, Philadelphia, addressed the Northampton County Medical Society, January 17, on "The General Practitioner and Everyday Dermatoses."——Dr. Frank H. Lahey, Boston, President-Elect of the American Medical Association, addressed the Lackawanna County Medical Society, Scranton, January 30, on "Surgery of the Stomach and Small Intestine."

Philadelphia

Program on Aviation Medicine.—The Philadelphia Laryngological Society had a program devoted to aviation medicine, February 4. The speakers were Comdr. John C. Adams, U. S. Navy, on "Aviation Medicine Today"; Comdr. John R. Poppen, U. S. Navy, "Otolaryngology and Physical Stresses in Modern Aviation"; Comdr. Travis S. Moring, U. S. Navy, "Aviation Ophthalmology"; Drs. Robert J. Hunter, "Experiences as a Flight Surgeon"; Alfred N. Richards, vice president for medical affairs, University of Pennsylvania, "General Considerations of Aviation Medicine," and Carl F. Schmidt, professor of pharmacology, University of Pennsylvania School of Medicine, "Recent Advances in Physiology Pertaining to Aviation Medicine."

VIRGINIA

Graduate Course in Specialties.—The seventh annual postgraduate course in ophthalmology and otolaryngology was held at the University of Virginia Department of Medicine, Charlottesville, December 10-13. The lecturers included Drs. Marvin F. Jones, New York; James Milton Robb, Detroit; Harry S. Gradle, Chicago; Frank B. Walsh, Baltimore, and Comdr. John R. Poppen, Bureau of Aeronautics, U. S. Navy.

Personal.—Dr. Bathurst B. Bagby, West Point, former director of the bureau of child health in the state health department, has been appointed city epidemiologist and chief health officer of Richmond on a temporary basis. Dr. William A. Browne resigned as epidemiologist and acting health officer to become health officer of Alexandria. The position of health officer had not been filled since the advent of a new city administration. Dr. Bagby retired from the state service in July 1940.——Dr. George A. Welchons, assistant director of Pine Camp Hospital, Brook Hill, city tuberculosis hospital for Richmond, has been appointed superintendent and medical director to succeed Dr. Percy E. Schools, resigned.

WASHINGTON

Surgical Meeting.—Dr. Allen O. Whipple, New York, was the guest speaker at the annual meeting of the Seattle Surgical Society at the King County Hospital, Seattle, January 31 and February 1. Dr. Whipple discussed the papers presented by local surgeons each morning and afternoon and made addresses at two dinner meetings on "Surgery of the Pancreas" and "Results of Decompression with Intestinal Intubation in Surgery of the Intestinal Tract."

Society News.—Drs. Rudolph G. Andres and George H. Anderson addressed the Spokane County Medical Society, Spokane, January 9, on "Intestinal Obstruction" and "Hyperventilation Syndrome" respectively.——Dr. Caspar W. Sharples, Seattle, addressed the Grays Harbor County Medical Society at its December meeting on "Differential Diagnosis of Abdominal Conditions."——Karl F. Meyer, Ph.D., San Francisco, addressed the Walla Walla Valley Medical Society, Walla Walla, January 16, on "Virus Diseases."——Dr. Frederick A. Slyfield, Seattle, addressed the Pierce County Medical Society, Tacoma, January 14, on "Diseases of the Chest."

GENERAL

Congress on Dental Education.—The Council on Dental Education of the American Dental Association will hold a Congress on Dental Education and Licensure at the Stevens Hotel, Chicago, February 15. The speakers will include:

Dr. Ray Lyman Wilbur, Stanford University, Calif., chairman of the Council on Medical Education and Hospitals of the American Medical Association, Professional Education and Licensure.
Dr. Charles Sidney Burwell, dean, Harvard Medical School, Boston, The Harvard Plan of Dental Education.
John T. O'Rourke, D.D.S., dean, University of Louisville School of Dentistry, The Aims of Dental Education.
Harold W. Alden, D.D.S., Northampton, Mass., chairman, National Board of Dental Examiners, The Functions and Methods of the National Board of Dental Examiners.
Morton H. Jones, D.D.S., secretary, Ohio State Dental Board, Columbus, The Aims of Licensure in Dentistry.
Edward S. Jones, Ph.D., professor of psychology, University of Buffalo, The Philosophy and Procedure of the Examining Process.
J. Ben Robinson, D.D.S., dean, Baltimore College of Dental Surgery of the University of Maryland, Functions of the Council on Dental Education.

Mid-South Post Graduate Assembly.—The fifty-sixth annual session of the Mid-South Post Graduate Assembly will be held in Memphis, Tenn., February 11-14 at the Hotel Peabody. The guest speakers will include:

Major Gen. James C. Magee, Washington, D. C., Medical Preparation for the Present Emergency.
Dr. Henry P. Wagener, Rochester, Minn., Diagnostic and Prognostic Significance of Retinal Glomerulonephritis.
Dr. Eldridge L. Eliason, Philadelphia, Surgical Aspects of Gastrointestinal Hemorrhage.
Dr. William D. Stroud, Philadelphia, Digitalis, Its Indications and Best Method of Administration.
Dr. Elmer L. Sevringhaus, Madison, Wis., Obesity, Types and Treatment.
Dr. Bret Ratner, New York, The Asthmatic Child.
Dr. Dallas B. Phemister, Chicago, Conservative Surgery in the Treatment of Sarcoma.
Dr. Marion A. Blankenhorn, Cincinnati, Nutritional Disorders of the Nervous System.
Dr. Leon Herman, Philadelphia, The Physiological and Clinical Significance of Renal Symptoms.
Dr. Verne C. Hunt, Los Angeles, Surgical Considerations of Obstructive Jaundice.

Dr. James L. Dunavant, Ripley, Tenn., is president of the assembly and Dr. Clyde M. Speck, New Albany, Miss., is president-elect.

Conference on Medical Service.—The fifteenth annual meeting of the National Conference on Medical Service, formerly the Northwest Regional Conference, will be held in the Red Lacquer Room, Palmer House, Chicago, Sunday, February 16. Dr. Forrest L. Loveland, Topeka, is president, and Dr. Harold M. Camp, Monmouth, Ill., secretary. The first session will be devoted to discussion of voluntary group medical programs with the following speakers: Mr. J. D. Laux, executive director, Michigan Medical Service, Detroit; Dr. William M. Hartman, Macomb, and Mr. J. George Crownhart, Madison, Wis. Medical preparedness will be discussed by Drs. Irvin Abell, Louisville; Morris Fishbein, Chicago, Editor of THE JOURNAL; Leonard G. Rowntree, chief, medical division, selective service system, Washington, D. C., and Olin West, Chicago, Secretary and General Manager of the American Medical Association. State medical societies' postgraduate programs will be discussed by Drs. Howard E. Snyder, Winfield, Kan., William A. O'Brien, Minneapolis, and Robert S. Berghoff, Chicago. Federal and state legislative problems will be presented, respectively, by Dr. Edward H. Cary, Dallas, and Mr. J. W. Holloway Jr., Chicago. Medical care for social security clients will be considered by Mr. Walter F. Finke, director, Minnesota Division of Social Welfare, department of social security, St. Paul; Dr. Alfred W. Adson, Rochester, Minn.; Mr. Walter G. Stumbo, Topeka, Kan., and Dr. Charles H. Phifer, Chicago. Mr. C. H. Wantz, president, Medical Exhibitors Association, Chicago, will discuss "The Annual Meetings from the Standpoint of the Exhibitor."

CORRECTION

"Vitamin Sweets."—In the editorial on this subject which appeared in THE JOURNAL for January 18, a footnote stated that the vitamin A concentrate used was probably that of the Eastman Kodak Company. We are informed that the Distillation Products, Inc., of Rochester, N. Y., took over the patents and work on this subject from the Eastman Kodak Company in June 1939. This company sells vitamin A concentrate in bulk to food and drug manufacturers. None is sold retail. The company states that it has supplied limited quantities of these concentrates to Dr. Newton, but the company has made no recommendation nor has it been active in any way in promoting "Vitamin Sweets."

Foreign Letters

LONDON

(From Our Regular Correspondent)

Dec. 14, 1940.

Temporary Registration for United States and Canadian Physicians

A defense regulation has been passed which enables physicians legally entitled to practice in any territory outside the United Kingdom to which the regulation is applied to be temporarily registered in the Colonial or Foreign Section of the Medical Register for a period not longer than that of the present emergency, if it is shown to the satisfaction of the General Council of Medical Education and Registration that the physicians fulfil the prescribed conditions. An order has been made by the council applying the regulation to each of the provinces of Canada and to the United States. The order prescribes as conditions of temporary registration that applicants shall be (1) British subjects or citizens of the United States, (2) shall be of good character and (3) shall hold a medical diploma granted in a province of Canada or in the United States which is recognized for the time being by the council for the purposes of the order as furnishing sufficient guaranty of the possession of the requisite professional knowledge and skill. The way is thus opened to our colleagues in Canada and the United States who wish to give practical expression to their belief that our cause is their cause by placing their services at the disposal of the British government as long as the emergency lasts.

End of Medical Reciprocity with Italy

At the same time as the Council announced this order it put an end to the order made forty years ago establishing medical reciprocity with Italy. The president stated that for the greater part of this long period Italy had taken privileges far more extensive than any that she gave. The right of persons already entered on the foreign list of the Medical Register by virtue of diplomas granted in Italy is not prejudiced by the new position.

War Economy in Dermatologic Prescribing

In a previous letter the disuse of drugs which have to be imported and the substitution for them of equivalents produced at home, in order to conserve cargo space for war purposes, was described. The special field of dermatologic prescribing has been dealt with by the Therapeutics Requirements Committee of the Medical Research Council in a memorandum of suggestions. It is pointed out that, for many of the purposes for which ointments are prescribed, pastes and creams are more satisfactory and they require only about half the amount of fatty basis. Fatty vehicles can sometimes be replaced by wet dressings (with or without mucilage), antiseptic paints and varnishes or powders. With regard to antiseptics, boric acid and iodine need not be used in dermatology. The amount of mercury used can be greatly reduced by limiting it to cases in which other antiseptics have not proved satisfactory. If the antiseptics were limited to aniline dyes, coal tar derivatives, salicylic acid, sulfur, ichthammol, resorcinol, dioxyanthranol, silver nitrate and tar, the treatment of most cutaneous diseases would not suffer much. For the treatment of ringworm, mercurials and iodine are rarely required, whereas a paste containing fuchsin and Whitfield's ointment of benzoic and salicylic acid are effective and freely available. If epidemics of scabies should occur, treatment will be most economical by dermatologists. Sulfur ointment still remains one of the most efficacious remedies. If benzyl benzoate is scarce, it had best be reserved for the treatment of children. For the treatment of pediculosis of the body or scalp, oily dressings are not essential, though of some value in pediculosis pubis.

The committee has divided dermatologic drugs into the same groups as in the previous memorandum: 1. Those readily available or essential—acriflavine, aniline dyes, benzoic acid, calamine, chloroform, coal tar, ether, hydrochloric acid, hydrogen peroxide, ichthammol, kaolin, saponated solution of cresol, phenol, resorcinol, salicylic acid, silver nitrate, sodium bicarbonate, sulfur, tannic acid, wool fat and zinc. 2. Drugs essential for certain purposes, to which they should be restricted. In the following list substitutes are given in parentheses: aluminum acetate (lead acetate), boric fomentations (saline compresses), chrysarobin (dioxyanthranol), iodine (proflavine, acriflavine, trinitrophenol, crystal violet or brilliant green), magnesium sulfate (sodium sulfate). 3. Drugs whose efficacy does not justify importation or manufacture in wartime—almond oil and sulfurated potash. For the latter, sulfur ointment or sulfurated lime could be substituted.

American Red Cross Aids British Children

By far the largest help from America to Britain, apart from military supplies, has been in the form of gifts from the American Red Cross, which amount to $12,500,000. Besides cash contributions the American Red Cross, which is organized in three thousand, seven hundred chapters covering the forty-eight states, has "Aid-to-Britain" groups making clothing of all kinds to help our war effort. Already thirty-five large country houses have been taken over as nursery homes for bombed London children. The cost of their maintenance is being borne by the junior branch of the American Red Cross —that is, by the children of America, who will also provide thirty thousand Christmas boxes for children bombed out of their houses and living in the shelters of London and other cities. Mr. Daniel Grant, chairman of the American Red Cross Committee in Great Britain, has declared that "the American people, through the American Red Cross, have made a great effort to help the people of Britain. It is an effort second only in importance to the supplies of munitions and aircraft reaching here from America."

The American Red Cross distributes its supplies through the British Red Cross and the Women's Voluntary Services. Some idea of the amount of help given is shown by a recent inventory of Mr. Grant, which reveals the promise of one hundred and thirty-six fully equipped mobile canteens, twenty of which are already in operation, twelve of which are working in London and take food every night to auxiliary fire service men, air raid wardens, police and first line shelters. Other gifts include one hundred and twenty thousand pairs of boots and shoes and a million garments for air raid victims. A quarter of a million yards of material has been purchased in Great Britain for the Women's Voluntary Service, who will work it up into garments. The British Red Cross has also received one hundred and ten ambulances and is promised another three hundred in the near future, ten complete roentgen ray units, thirteen fully equipped operating tables, large quantities of blood plasma given by people in America, all kinds of medical supplies, hospital equipment and clothing.

Leiden University in the Netherlands Is Closed

News has been received in London of the closure by the Germans of the famous university of Leiden. The reason given is that the students have been "obstructive," which in ordinary language means that the pursuit of truth in accordance with the tradition upheld by Leiden for more than three and one-half centuries is inconsistent with nazi doctrines. It may be recalled that Boerhaave, one of the fathers of modern medicine, taught at Leiden and attracted vast audiences from all over Europe. Edinburgh's great medical school can be

traced to Boerhaave's lecture room. In Leiden's early days Scaliger added to its glory and in the present day Einstein has done so. The physicist Lorentz was proud of his Leiden professorship, and there at the beginning of this century Omnes carried out his famous experiments on gases at extremely low temperatures, culminating in his liquefaction of helium. Truly Europe is witnessing an eclipse of her higher civilization.

Masks in the Prevention of Infection

A committee of the House of Commons has recommended the wearing of a simple form of mask in air raid shelters during epidemics, with the object of preventing infection. During the fatal epidemic of influenza which followed the last great war, masks were worn in some hospitals by all who entered the wards. Though the infection was most virulent, physicians, nurses and attendants escaped with few exceptions. The masks consisted only of a pad of white gauze secured by tapes. As the season of influenza epidemics is near, it has been suggested that the dislocation of industry caused every year by this disease could be reduced to a minimum and the millions of working hours—so important just now—could be saved if masks were introduced into factories and workshops as well as into air raid shelters.

The Prevention of Diphtheria

In reply to a question in the House of Commons by Prof. A. V. Hill (the physiologist), the minister of health stated that the annual number of cases of diphtheria in England and Wales is about 60,000, of which 54,000 occur in children under the age of 15. The average number of children under 15 who die from diphtheria is 2,700. The average number of hospital beds occupied by diphtheria patients is five thousand, and the annual cost of the hospital treatment is $5,000,000. The minister stated that experience in Canada and the United States showed that the disease can be almost entirely eliminated by the immunization of children. In view of the fact that children are now being freely moved from one area to another (in the evacuation due to air raids), Professor Hill asked whether the necessary agents for preventive inoculation might not now be provided as a national charge instead of one on the local authorities. Also in view of concern as to the spread of infection in crowded air raid shelters would the Ministry of Health take more active steps to protect the child population against diphtheria. The minister replied that his policy was to encourage local authorities to provide facilities for immunization and to do their best to persuade parents to take advantage of them. The cost of the necessary material in the present war conditions would be reimbursed to the local authorities by the government.

Sir Henry Dale President of the Royal Society

The highest scientific honor in this country, the presidency of the Royal Society, has been conferred on Sir Henry Dale in succession to Sir William Bragg. Since 1663 there have been forty-four presidents of the Royal Society, and Dale is the eighth member of the medical profession to hold the office. He has never engaged in practice as a physician but has devoted himself to research. His medical education took place at St. Bartholomew's Hospital and University College. From 1904 to 1914 he was director of the Wellcome Physiological Research Laboratories. He then was appointed head of the department of biochemistry and pharmacology of the Medical Research Council. In 1928 he was made director of the National Institute of Medical Research, which he still is.

His first step in the researches which have made him famous was his investigation of the action of acetylcholine in 1914, but not till 1929 was he able, in collaboration with Dudley, to isolate it from an animal organ in quantities sufficient to be identified chemically. Observations on the frog's heart by Loewi and further researches by Dale, with other collaborators, led to the knowledge that acetylcholine is the substance liberated at parasympathetic endings and the endings of preganglionic fibers in autonomic ganglions. It was later shown that it is liberated also at the endings of voluntary motor nerves. Dale introduced the terms "cholinergic" and "adrenergic" to describe action of the nerve fibers of the autonomic system in terms of chemical function. Another research of fundamental importance, in collaboration with Berger and Laidlaw, was on the active principles of ergot, which led to the identification of the alkaloid ergonovine. From his work on ergot developed his researches on the action of histamine and its analogy with surgical shock, which were carried out during the last war. His training and direction of workers in the field of biochemistry have been of far reaching importance. In 1919 he delivered the Herter lecture at the Johns Hopkins University. In 1936 he shared the Nobel prize for medicine.

Marriages

ALBERT JOSEPH ORLOSKY, Arlington, Va., to Miss Nancy Elise Conley of Washington, D. C., in October 1940.

GEORGE RUDOLPH LAUB, New Bern, N. C., to Miss Harriet Elizabeth Stith of Columbia, S. C., in October 1940.

PAUL L. SINGER, Des Moines, Iowa, to Miss Shirley E. Ellis of Hillsdale, Mich., in Chicago, Oct. 26, 1940.

HOMER JACKSON HANCOCK, Welch, W. Va., to Miss Harriet Loyd Hudgins of Warrenton, N. C., Oct. 26, 1940.

KENDALL O. KENNEDY, Columbus, Ohio, to Miss Laura K. Campbell in Paw Paw, Mich., in October 1940.

FRANK MATTHEWS PARISH, Brunswick, Ga., to Miss Martha Elizabeth Mobley of Atlanta in October 1940.

WILLIAM EDWARD ADAIR JR. to Miss Lucy Blake Ward, both of Wilmington, N. C., in October 1940.

JAMES MONTELEONE CIARAVELLA, New Orleans, to Miss Frances Anzalone at Independence recently.

DANIEL SMITH CURRIE JR., Parkton, N. C., to Miss Marion Cox Wood near Vanceboro, Oct. 26, 1940.

ANDREW M. JAMISON JR., Spartanburg, S. C., to Miss Evelyn Byrd Hardin in Cincinnati, Oct. 27, 1940.

WILLIAM LOVELL WRIGHT, West Liberty, Ky., to Miss Eva Sara Murphy of Lexington, Oct. 12, 1940.

DUDLEY Y. OLDHAM, Houston, Texas, to Miss Cornelia Cobb of Longville, La., Oct. 20, 1940.

HOYT R. ALLEN to Mrs. Martha Branham, both of Little Rock, Ark., at Benton, Oct. 19, 1940.

GENE L. TEPLEY to Miss Agnes Josephine Eusterbrock, both of Howells, Neb., Oct. 26, 1940.

JOHN M. COOK, Pittsburgh, to Miss Velma Elizabeth Bowser of Beaver Falls, Pa., in October 1940.

BASSEL NELSON BLANTON, Temple, Texas, to Miss Frances Carol Crain of Waco, Oct. 30, 1940.

ARTHUR PARK MCGINTY, Atlanta, Ga., to Miss Murray Smith of Birmingham, Ala., recently.

PAUL E. DINGLE, New Castle, Ind., to Miss Marian Atchison of East Palestine, Ohio, recently.

LELAND B. GOULD, Coquille, Ore., to Miss Mabel E. Henderson of Portland in October 1940.

JOHN GRAHAM NORRIS, Farmerville, La., to Miss Mary Inez Taylor in Monroe in October 1940.

ALAN STANFORD HORWITZ, New York, to Miss Charlotte Vangrov of Dayton, Ohio, recently.

JOHN E. ALLGOOD JR. to Miss Virginia Marie Schiller, both of Petersburg, Ohio, Oct. 21, 1940.

CHARLES CRAIG GASS, Kearney, Neb., to Miss Doris Edna Griffiths of Omaha, Oct. 19, 1940.

CLARENCE F. KELLY JR., Duquoin, Ill., to Miss Lillian Masters of Butler in October 1940.

WILLIAM MCCONNELL JONES, Gastonia, N. C., to Miss Elizabeth Garlington, Oct. 14, 1940.

LEWIS HOWARD MCDONALD to Miss Lois Reeves, both of Atlanta, Ga., Oct. 12, 1940.

Deaths

Carl Roger Darnall ✠ Brigadier General, United States Army, retired, Washington, D. C., died, January 18, in the Walter Reed General Hospital of arteriosclerosis, aged 73. General Darnall was born Dec. 25, 1867 in Weston, Texas; he graduated from the Jefferson Medical College of Philadelphia in 1890 and the Army Medical School in 1897. He entered the military service Oct. 27, 1896 and was appointed captain and assistant surgeon Oct. 26, 1901, major April 23, 1908, lieutenant colonel July 1, 1916 and colonel May 15, 1917. His first service was with the 23d infantry at Fort Clark, Texas. In 1900 he was on duty at the United States Military Hospital in Havana, Cuba. From May 1900 to April 1901 he served as operating surgeon and pathologist on the hospital ship *Relief*. He commanded the Military Hospital at Iloilo, Philippine Islands, 1901-1902; in June 1902 he returned to the United States and was on duty in the Office of the Surgeon General, Washington, D. C. From June 1903 until 1913 he was on duty at the Army Medical School, serving as adjutant and secretary of the faculty, instructor in sanitary chemistry and operative surgery. During that period he was in charge of the medical supply depot, Washington, D. C., a member of the army examining board and of the joint board of army and navy medical officers. Brigadier General Darnall served in the Philippine Islands from April 1914 until July 1916 at the Department Hospital in Manila and at the Medical Supply Depot. Returning to the United States in August 1916, he again served in the Office of the Surgeon General as executive officer. In December 1922 he was transferred to Hawaii, where he served as department surgeon. In August 1925 he was ordered to duty in the Office of the Surgeon General, where he served as executive officer until 1929, when he was appointed assistant surgeon general with rank of brigadier general, commanding the Army Medical Center. Brigadier General Darnall was awarded the Distinguished Service Medal. He retired Dec. 31, 1931 by operation of law. He was a fellow of the American College of Surgeons. In 1910 he originated the liquid chlorination of water for the safeguarding of water supplies.

Paul Ferdinand Schilder ✠ New York; Medizinische Fakultät der Universität Wien, Austria, 1909; research professor of psychiatry at the New York University College of Medicine; member of the American Neurological Association, American Psychiatric Association and the American Psychopathological Association; clinical director of the psychiatric division of Bellevue Hospital; served in the Austrian Army during the World War; author of "Introduction to a Psychoanalytic Psychiatry" and several books published in Berlin and Vienna; aged 54; died, Dec. 8, 1940, in the Misericordia Hospital of injuries received when he was struck by an automobile.

Louis Casper Duncan ✠ Colonel, United States Army, retired, St. Petersburg, Fla.; Kansas Medical College, Topeka, 1896; demonstrator and assistant professor of anatomy at his alma mater from 1896 to 1898; veteran of the Spanish-American War; entered the medical corps of the Army as a first lieutenant on Oct. 27, 1902 and graduated the following year from the Army Medical School; reached the grade of lieutenant colonel on May 15, 1917 and was retired on March 2, 1920; during the World War was given the temporary grade of colonel and was advanced to that grade on the retired list on June 21, 1930; aged 71; died, Oct. 19, 1940, of bronchopneumonia.

William S. Smith, Baltimore; University of Maryland School of Medicine, Baltimore, 1883; clinical professor of gynecology at his alma mater, now the University of Maryland School of Medicine and College of Physicians and Surgeons; professor of gynecology at the Maryland Medical College from 1898 to 1913; surgeon, city police department from 1888 to 1898; examiner, state board of labor and statistics from 1916 to 1919; aged 80; for many years consultant in gynecology at the E. C. Hazard Hospital, Long Branch, N. J., and on the staff of the Franklin Square Hospital, where he died, Dec. 9, 1940, of uremia due to carcinoma of the prostate.

Clelia Duel Mosher, Stanford University, Calif.; Johns Hopkins University School of Medicine, Baltimore, 1900; assistant professor of personal hygiene, Stanford University, from 1910 to 1922, associate professor from 1922 to 1928, professor, 1928-1929 and professor emeritus since 1929, and medical adviser of women from 1910 to 1929; medical investigator, children's bureau, and assistant medical adviser and later associate medical director, Bureau of Refugees and Relief, American Red Cross in France, from 1917 to 1919; aged 77; died, Dec. 22, 1940.

Karl Sigismund Blackwell ✠ Richmond, Va.; University College of Medicine, Richmond, 1906; professor of otolaryngology, Medical College of Virginia; fellow of the American College of Surgeons; past president and vice president of the Virginia Society of Ophthalmology and Otolaryngology; formerly vice president of the Medical Society of Virginia; past president of the Richmond Academy of Medicine; on the staff of the Hospital Division of the Medical College of Virginia; aged 61; died, Dec. 26, 1940, of coronary thrombosis.

Robert Pelton Wadhams ✠ New York; University and Bellevue Hospital Medical College, New York, 1906; professor of clinical surgery at his alma mater, now known as the New York University College of Medicine; fellow of the American College of Surgeons; served during the World War; attending surgeon, Bellevue Hospital; associate attending surgeon, French Hospital; consulting surgeon, Charlotte Hungerford Memorial Hospital, Torrington, Conn.; aged 61; died, Dec. 16, 1940, of heart disease.

de Wayne Greenwood Richey ✠ Pittsburgh; University of Pittsburgh School of Medicine, 1915; assistant professor of laryngology and rhinology at his alma mater; member of the American Association of Pathologists and Bacteriologists; fellow of the American College of Surgeons; served during the World War; aged 48; on the staffs of the Mercy Hospital, Pittsburgh, and the Columbia Hospital, Wilkinsburg, Pa., where he died, Dec. 5, 1940, of portal cirrhosis of the liver.

John Templeton Bowen, Boston; Harvard Medical School, Boston, 1884; member of the Massachusetts Medical Society; instructor of dermatology at his alma mater from 1896 to 1912, assistant professor from 1902 to 1907, Edward Wigglesworth professor from 1907 to 1912 and since 1912 professor emeritus at his alma mater; for many years on the staff of the Massachusetts General Hospital; aged 83; died, Dec. 3, 1940, of pyelonephritis.

Percy Hypes Swahlen ✠ St. Louis; St. Louis University School of Medicine, 1903; associate professor of gynecology and obstetrics at his alma mater; fellow of the American College of Surgeons; past president of St. Louis Medical Society; obstetrician, St. Ann's Maternity and Mount St. Rose hospitals; visiting obstetrician and gynecologist, St. Louis City Hospital; gynecologist, St. John's Hospital; aged 63; died, Dec. 10, 1940, of coronary thrombosis.

Louis Emmitt Brown ✠ Akron, Ohio; Baltimore Medical College, 1903; member of the American Academy of Ophthalmology and Otolaryngology and the American Laryngological Association; fellow of the American College of Surgeons; member of the city board of health; served during the World War; past president of the Akron Academy of Ophthalmology and Otolaryngology; on the staff of the City Hospital; aged 59; died, Dec. 11, 1940.

Ogden Matthias Edwards Jr. ✠ Pittsburgh; Columbia University College of Physicians and Surgeons, New York, 1896; professor of pediatrics at the University of Pittsburgh School of Medicine from 1909 to 1919 and acting dean from 1917 to 1919; formerly a member of the staffs of the Western Pennsylvania Hospital, St. Francis Hospital and the Children's Hospital; aged 71; died, Dec. 28, 1940.

Arthur Elias Leitch ✠ Saginaw, Mich.; Detroit College of Medicine, 1893; past president and secretary of the Saginaw County Medical Society; served during the World War; aged 68; on the staffs of Saginaw General Hospital, St. Luke's Hospital and St. Mary's Hospital, where he died, Dec. 9, 1940, of abscess of the right kidney.

Walter Scott Turnbull, Vancouver, B. C., Canada; University of Toronto Faculty of Medicine, 1903; member of the North Pacific Surgical Association; past president of the British Columbia Medical Association; for many years on the staff of the Vancouver General Hospital and the Grace Hospital; aged 62; died in November 1940.

Edward Leo Zimmerman ✠ Eugene, Ore.; Jefferson Medical College of Philadelphia, 1912; served during the World War; past president of the Oregon State Medical Society and the Lane County Medical Society; on the staff of the Sacred Heart Hospital; aged 51; died, Dec. 2, 1940, of arteriosclerosis, thrombosis and myocarditis.

Joseph Sylvester Miller, York, Pa.; College of Physicians and Surgeons, Baltimore, 1880; member of the Medical Society of the State of Pennsylvania; past president of the York County Medical Society; served on the staff of the York Hospital in various capacities; aged 84; died, Dec. 8, 1940, of thrombosis and gangrene.

George D. Lummis, Middletown, Ohio; Medical College of Ohio, Cincinnati, 1884; president of the International Health Officers Association; for more than half a century health commissioner of Middletown; for many years member of the Ohio Public Health Council; aged 77; died, Dec. 26, 1940, of coronary thrombosis.

Charles F. Zeller ✠ Jerome, Idaho; University Medical College of Kansas City, Mo., 1903; past president of the Southside Medical Society; on the staff of St. Valentine's Hospital, Wendall; aged 60; died, Dec. 1, 1940, in Rochester, Minn., of carcinoma of the colon and peritonitis.

Arthur Raphael Brennan, Brooklyn; Baylor University College of Medicine, Dallas, Texas, 1921; member of the Medical Society of the State of New York; on the staffs of St. Peter's Hospital and St. Mary's Hospital; aged 44; died, Dec. 11, 1940, of coronary thrombosis.

Clarence Ross Hepler ✠ Parsons, Kan.; University Medical College of Kansas City, Mo., 1902; member of the American Psychiatric Association; at one time health officer of Cherokee County and Sedgwick County; aged 66; died, Nov. 17, 1940, of coronary thrombosis.

A. J. Markley, Belvidere, Ill.; Bennett College of Eclectic Medicine and Surgery, Chicago, 1881; member and for many years treasurer of the Illinois State Medical Society; aged 82; died, Dec. 13, 1940, in St. Joseph's Hospital of carcinoma of the transverse colon.

William Langdon Haskell ✠ Lewiston, Maine; Medical School of Maine, Portland, 1894; fellow of the American College of Surgeons; served during the World War; on the staff of St. Mary's General Hospital; aged 70; died, Dec. 9, 1940, of arteriosclerosis.

Edward William Bing, Chester, Pa.; Jefferson Medical College of Philadelphia, 1877; member of the Medical Society of the State of Pennsylvania; also a pharmacist; aged 84; formerly on the staff of the Chester Hospital, where he died, Dec. 10, 1940.

Henry Augustus Kurth ✠ Schenectady, N. Y.; College of Physicians and Surgeons, medical department of Columbia College, New York, 1890; for many years on the staff of the Ellis Hospital; aged 77; died, Dec. 7, 1940, of carcinoma of the prostate.

J. Sumner Teter, Toledo, Ohio; Starling Medical College, Columbus, 1904; member of the Ohio State Medical Association; for many years on the staff of the Robinwood Hospital; served during the World War; aged 63; died, Dec. 6, of cerebral hemorrhage.

William George Carnathan ✠ Butler, Ala.; Medical College of Alabama, Mobile, 1905; president of the Choctaw County Medical Society; formerly county health officer; aged 58; died, Nov. 30, 1940, in Riley's Hospital, Meridian, of intestinal obstruction.

Herman Verplanck Hoffman ✠ San Francisco; University of California Medical Department, San Francisco, 1905; served during the World War; on the staffs of St. Mary's Hospital and Dante Hospital; aged 58; died, Nov. 16, 1940, of coronary disease.

Thomas Francis Maher ✠ Newington, Conn.; Yale University School of Medicine, New Haven, 1901; served during the World War; on the staff of the Veterans Administration Facility; aged 62; died, Dec. 18, 1940, of chronic myocarditis.

Jacob Kinzer Shell, Philadelphia; University of Pennsylvania Department of Medicine, Philadelphia, 1881; aged 78; died, Dec. 10, 1940, in the Presbyterian Hospital of hypertrophy of the prostate and arteriosclerotic heart disease.

Norman Clyde Mills, Clarion, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1902; aged 63; died, Dec. 6, 1940, in the Brookville (Pa.) Hospital of injuries received when he was struck by an automobile.

Carlo D. Martinetti ✠ Orange, N. J.; Regia Universita degli Studi di Siena Facoltà di Medicina e Chirurgia, Italy, 1903; on the staff of the Community Hospital, Montclair; aged 62; died, Dec. 9, 1940, of cerebral hemorrhage.

Arthur Rockwell Addy, Brooklyn; Columbia University College of Physicians and Surgeons, New York, 1899; served during the World War; aged 70; died, Dec. 13, 1940, in the Kings County Hospital of arteriosclerosis.

George Walley Heck, Bethlehem, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1907; member of the Medical Society of the State of Pennsylvania; aged 59; died, Dec. 9, 1940, of cerebral hemorrhage.

Greene L. Johnson ✠ Harrodsburg, Ky.; Hospital College of Medicine, Louisville, 1907; past president of the Mercer County Medical Society; formerly county health officer; aged 56; died, Dec. 4, 1940, of carcinoma.

Charles M. Seaton, Morrisonville, Ill.; Illinois Medical College, Chicago, 1902; member of the Illinois State Medical Society; aged 64; died, Dec. 4, 1940, in St. Vincent Hospital, Taylorville, of angina pectoris.

L. Lester Self, Cherryville, N. C.; University College of Medicine, Richmond, 1901; aged 62; died, Dec. 4, 1940, in the Charlotte (N. C.) Eye, Ear and Throat Hospital of myocarditis and coronary thrombosis.

Ned Snyder, Brownwood, Texas; Fort Worth School of Medicine, Medical Department of Fort Worth University, 1909; member of the State Medical Association of Texas; aged 55; died in November 1940.

William Edward McGuire, Cottonwood, Ill.; Barnes Medical College, St. Louis, 1899; member of the Illinois State Medical Society; for many years county coroner; aged 67; died, Dec. 10, 1940, of heart disease.

Robert Lewis Segrest, Wisner, La.; Medical Department of Tulane University of Louisiana, New Orleans, 1907; member of the Louisiana State Medical Society; aged 58; died, Nov. 29, 1940.

Tilton Edwin Tillman ✠ San Francisco; Cooper Medical College, San Francisco, 1902; served during the World War; aged 59; died, Dec. 5, 1940, of coronary occlusion and pulmonary infarction.

Samuel Miles Robinson, Orlando, Fla.; Hahnemann Medical College and Hospital of Philadelphia, 1912; aged 84; died, Dec. 4, 1940, of typhus fever, chronic myocarditis and arteriosclerosis.

Nathan David Garnsey ✠ Kinderhook, N. Y.; Albany (N. Y.) Medical College, 1891; served during the World War; aged 76; died, Dec. 4, 1940, of cerebral thrombosis and arteriosclerosis.

Amos Carson Duncan, Forest City, N. C.; North Carolina Medical College, Charlotte, 1919; aged 46; died, Dec. 10, 1940, in Hollandale, Fla., of mesenteric thrombosis and cirrhosis of the liver.

John Joseph Kowarskas, Chicago; Chicago Medical School, 1927; member of the Illinois State Medical Society; aged 42; died, Dec. 14, 1940, in the Holy Cross Hospital of diverticulitis.

Frank R. Shoemaker, Hollidaysburg, Pa.; Medico-Chirurgical College of Philadelphia, 1895; aged 66; died, Dec. 2, 1940, in the Nason Hospital, Roaring Spring, of septicemia.

James Thruston Wolfe ✠ Washington, D. C.; George Washington University School of Medicine, Washington, 1908; aged 59; died, Dec. 8, 1940, of coronary occlusion.

James Pringle Crawford, Nashville, Tenn.; University of Maryland School of Medicine, Baltimore, 1893; served during the World War; aged 73; died, Nov. 25, 1940.

Joseph S. Lehman, Midway, Ky.; Cleveland Medical College, 1896; aged 71; died, Dec. 13, 1940, in the Good Samaritan Hospital, Lexington, of ruptured aneurysm.

Lee A. Wixsom ✠ Chicago; Chicago Medical School, 1918; aged 48; died, Dec. 9, 1940, in the Englewood Hospital of septicemia, pyemia and diabetes mellitus.

William Edmund Aughinbaugh, New York; National University Medical Department, Washington, D. C., 1897; also a lawyer; aged 69; died, Dec. 18, 1940.

James Balance Wood, St. Louis; St. Louis College of Physicians and Surgeons, 1917; served during the World War; aged 47; was found dead, Nov. 23, 1940.

Albert Sidney Steagall, Abbeville, Ala.; Medical College of Alabama, Mobile, 1888; formerly bank president; aged 74; died, Nov. 28, 1940, of heart disease.

Benjamin Lucas Norwood, McBee, S. C.; Louisville (Ky.) Medical College, 1887; aged 74; died, Dec. 8, 1940, of bronchopneumonia and nephritis.

Thomas C. Williams, New York; New York Homeopathic Medical College, New York, 1881; aged 82; died, Dec. 5, 1940, of myeloid leukemia.

William Fraser Mackay, Port Washington, B. C., Canada; University of Toronto Faculty of Medicine, 1900; aged 70; died in November 1940.

Lytle Caldwell Adams, La Grange, N. C.; North Carolina Medical College, Davidson, 1903; aged 63; died, Dec. 8, 1940, of heart disease.

Correspondence

ACUTE APPENDICITIS IN MILITARY HOSPITALS

To the Editor:—An extensive experience in the management of acute appendicitis during the World War led to the publication of an article entitled "Immediate Surgical Management of Acute Appendicitis in Military Hospitals" (*Surg., Gynec. & Obst.* **28**:303 [March] 1919), suggesting a possible relationship between the onset of this condition in those cases in which there is a history of previous attacks and the method of administering the triple typhoid vaccine.

In view of the fact that a new army is being inducted into service, it seems to me that this article carries some conclusions that may be of importance, especially to the younger medical officers of the army. I would therefore call special attention to the lowering of the white blood cell count following the administration of triple typhoid vaccine, with a lower white cell count at the onset of an attack of acute appendicitis.

The blood picture sometimes puzzled medical officers in making a prompt diagnosis of acute appendicitis. Any factor which may delay a decision in making a prompt diagnosis in acute appendicitis is hazardous and must be corrected in order that surgery may not be delayed. I shall not attempt to discuss the relative importance of examinations of the blood as one of the factors in making a prompt diagnosis in acute appendicitis; suffice it to say that it may be of paramount importance in certain diagnostic decisions in acute abdominal conditions.

Hugh McKenna, M.D., Chicago.

ROLE OF LACTIC ACID IN DENTAL CARIES

To the Editor:—In The Journal of January 4 there is a communication from Dr. J. Lewis Blass, who in Correspondence discusses the studies of Neuwirth and Klosterman on the production of lactic acid by oral micro-organisms after the introduction of concentrated carbohydrate into the mouth. Dr. Blass states: "Control experiments by these workers demonstrate that this rapid production of lactic acid in the oral cavity can be ascribed to the activity of oral micro-organisms. Thus, for the first time now there is not only a demonstration of the production of acids in the oral cavity but also a demonstration of the production of a definite acid—lactic acid."

Dr. Blass mentions that Neuwirth and Klosterman (*Proc. Soc. Exper. Biol. & Med.* **45**:464 [Oct.] 1940) employed the ultramicro method for lactic acid developed by Muntz and myself, but he neglects to point out that subsequent to the development of this new technic Muntz and I determined the quantity of lactic acid in various types of carious lesions (*J. Dent. Research* **18**:259, 1939). Later, in the course of investigations with Bradel on the metabolism of dental plaque material we demonstrated the production of lactic acid from dextrose by plaques (abstracts of the Dec. 30, 1939 Proceedings of the Subsection on Dentistry, American Association for the Advancement of Science, reprinted in *J. Am. Coll. Dentists* **7**:80 [March-June] 1940; also see *Proc. Soc. Exper. Biol. & Med.* **45**:104 [Oct.] 1940). We have also shown the capacity of dental plaque material to produce lactic acid from dextrose, fructose, sucrose, maltose and starch (*J. Dent. Research* **19**:473 [Oct.] 1940).

Dr. Blass appears to stress a point of no great significance, i. e. the well known ability of certain oral micro-organisms to produce lactic acid. The important problem is to establish the precise role played by this acid in the chemopathogenesis of human dental caries. We have developed a sufficiently sensitive and specific lactic acid method for investigation of the role of lactic acid in dental caries. However, despite the investigations conducted with this method here, we feel that the question is still unanswered. For the time being it seems best to regard the lactic acid produced by oral micro-organisms or dental plaques as an index of their metabolic activities rather than as the only proved agent in the chemopathogenesis of dental caries.

Benjamin F. Miller, M.D.,
Walter G. Zoller Memorial Dental
Clinic and the Department of
Medicine, University of Chicago.

AMERICAN FEDERATION FOR CLINICAL RESEARCH

To the Editor:—The organization of a society to be called the American Federation for Clinical Research has been proposed, and the idea is meeting with an enthusiastic reception. It is to be a society of young men and women interested in and carrying on clinical investigation. There will be two classes of membership: (*a*) club and (*b*) individual. A club membership is for any group of persons concerned with investigation in clinical medicine or allied sciences. An individual membership is for any one who has completed a meritorious investigation in these fields and is interested in continuing investigation. It is proposed to limit admission to individual membership to persons under 40 years of age. "Clubs" may be formed with membership of any age at clinics, hospitals or medical schools acting individually or as groups in cities, states or provinces or groups of states of the United States and Canada. "Clubs" will meet as frequently as seems desirable. There will be one general meeting with a scientific program, held in rotation in different parts of the United States and Canada. Annual dues probably will not exceed $1. The organization meeting will be held at Haddon Hall, Atlantic City, N. J., on Monday, May 5. For those desiring to become individual members application blanks will be sent on request, mailed to Dr. Henry A. Christian, 1731 Beacon Street, Brookline, Mass., who is acting for a group of fourteen physicians who in 1908 participated in the organization of the American Society for the Advancement of Clinical Investigation. Questions regarding club membership may be similarly addressed.

Henry A. Christian, M.D., Brookline, Mass.

TUBERCULOSIS CARE AT BELLEVUE

To the Editor:—In Queries and Minor Notes (The Journal, Dec. 28, 1940) your correspondent conveys a misapprehension of practices at Bellevue Hospital in the treatment of Negroes with tuberculosis. In the Tuberculosis Service of this institution uniform criteria are followed in all cases in the use of collapse therapy. Among these criteria is an estimate of the patient's natural resistance, and it sometimes happens on this account that collapse therapy is used earlier for a Negro than it would be for a white patient with a similar lesion. On the other hand, the proportion of cases of acute pneumonic tuberculosis admitted to this service is higher among Negroes than among white patients. It is generally understood that the indiscriminate employment of collapse therapy for such forms of the disease may be harmful rather than helpful; therefore artificial pneumothorax and other mechanical procedures, when indicated, are used with extraordinary caution; in many cases such treatment is postponed until the acute inflammatory reactions have subsided.

J. Burns Amberson Jr., M.D., New York.

Medical Examinations and Licensure

COMING EXAMINATIONS

BOARDS OF MEDICAL EXAMINERS
BOARDS OF EXAMINERS IN THE BASIC SCIENCES

Examinations of boards of medical examiners and boards of examiners in the basic sciences were published in THE JOURNAL, February 1, page 434.

NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: Parts I and II. Various centers, February 10-12. Exec. Sec., Mr. Everett S. Elwood, 225 S. 15th St., Philadelphia.

EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY: *Oral.* Part II, Cleveland, May 31-June 1. Final date for filing application is April 1. Sec., Dr. Paul M. Wood, 745 Fifth Ave., New York.

AMERICAN BOARD OF INTERNAL MEDICINE: *Oral.* April, in advance of the meeting of the American College of Physicians and June, in advance of the meeting of the American Medical Association. *Written.* Oct. 20. Final date for filing application is Sept. 1. Sec., Dr. William S. Middleton, 1301 University Ave., Madison, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: *Written.* Philadelphia, June 6-7. Sec., Dr. R. Glen Spurling, 404 Brown Bldg., Louisville, Ky.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: Part II, Groups A and B, Cleveland, May 28-June 1. Final date for filing application is March 15. Sec., Dr. Paul Titus, 1015 Highland Bldg., Pittsburgh.

AMERICAN BOARD OF OPHTHALMOLOGY: *Oral.* Cleveland, May or June. Sec., Dr. John Green, 6830 Waterman Ave., St. Louis.

AMERICAN BOARD OF OTOLARYNGOLOGY: *Oral and Written.* Cleveland, May 31-June 2. Final date for filing application is March 1. Sec., Dr. W. P. Wherry, 1500 Medical Arts Building, Omaha.

AMERICAN BOARD OF PATHOLOGY: *Oral and Written.* Cleveland, June 2-3. Final date for filing application is May 1. Sec., Dr. F. W. Hartman, Henry Ford Hospital, Detroit.

AMERICAN BOARD OF PEDIATRICS: Chicago, May 18, following the Region III meeting of the American Academy of Pediatrics. Boston, Oct. 12, immediately following the annual meeting of the American Academy of Pediatrics. Sec., Dr. C. A. Aldrich, 707 Fullerton Ave., Chicago.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: *Oral.* Washington, May 2-3. Final date for filing application is Feb. 22. Sec., Dr. Walter Freeman, 1028 Connecticut Ave., N.W., Washington, D. C.

AMERICAN BOARD OF RADIOLOGY. *Oral.* Cleveland, May 30-June 1. Final date for filing application is April 15. Sec., Dr. Byrl R. Kirklin, 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF SURGERY: Part II. *Oral.* San Francisco, Feb. 18-19. *Written.* Part I. Various centers, April 2. Sec. Dr. J. Stewart Rodman, 225 South Fifteenth St., Philadelphia.

Connecticut November Report

Dr. Thomas P. Murdock, secretary, Connecticut Medical Examining Board, reports the written examination for medical licensure held at Hartford, Nov. 12-13, 1940. The examination covered 9 subjects and included 70 questions. An average of 75 per cent was required to pass. Thirty-two candidates were examined, 14 of whom passed and 18 failed. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
Yale University School of Medicine	(1939) 78.6,	(1940)	78.9*
Rush Medical College		(1940)	76.6
Johns Hopkins Univ. School of Med.	(1939) 75, 85.1,	(1940)	78.1
University of Maryland School of Medicine and College of Physicians and Surgeons		(1940)	75.1*
Harvard Medical School		(1939)	79*
University of Michigan Medical School		(1938)	81
Washington University School of Medicine		(1937)	75
Univ. of Rochester School of Medicine and Dentistry		(1940)	85.5
Marquette University School of Medicine		(1940)	75
University of Western Ontario Medical School		(1938)	75.1
Universität Leipzig Medizinische Fakultät		(1932)	75

School	FAILED	Year Grad.	Number Failed
Georgetown University School of Medicine		(1937)	1
Marquette University School of Medicine		(1940)	1
Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin		(1924)	1
Ludwig-Maximilians-Universität Medizinische Fakultät, München		(1920), (1923)	2
Medizinische Fakultät der Universität Wien		(1938)	1
Univ. Heidelberg Medizinische Fakultät		(1920), (1922)	2
Magyar Királyi Erzsébet Tudományegyetem Orvostudományi, Pecs		(1932)	1
Magyar Királyi Pázmány Petrus Tudományegyetem Orvosi Fakultasa, Budapest		(1938)	1
Regia Università degli Studi di Bologna. Facoltà di Medicina e Chirurgia		(1937)	1
Regia Università degli Studi di Padova. Facoltà di Medicina e Chirurgia		(1930)	1
Regia Università degli Studi di Roma. Facoltà di Medicina e Chirurgia		(1937)	1
Regia Università di Napoli Facoltà di Medicina e Chirurgia		(1938)	1
Universität Bern Medizinische Fakultät		(1937)	1
Université de Genève Faculté de Médecine		(1935)	1
Osteopaths†			2

Thirty physicians were successful in the oral examination for endorsement applicants held at Hartford, November 26. The following schools were represented:

School	PASSED	Year Grad.	Endorsement of
Yale University School of Medicine	(1935),* (1937, 2)		N. B. M. Ex.
George Washington University School of Medicine		(1937)	Maine
College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois		(1906)	Illinois
Johns Hopkins University School of Medicine		(1917)*	Maryland, (1937) N. B. M. Ex.
University of Maryland School of Medicine and College of Physicians and Surgeons		(1936)	Maryland
Boston University School of Medicine	(1936), (1937),*	(1938)*	N.B.M.Ex.
Harvard Medical School		(1914)*	Rhode Island, (1936) New York
Tufts College Medical School		(1938), (1939)*	N.B.M.Ex.
University of Nebraska College of Medicine		(1935)	Nebraska
Columbia Univ. College of Physicians and Surgeons		(1912)	New York
Cornell Univ. Med. College	(1924), (1935)	New York, (1938)	N. B. M. Ex.
Long Island College Hospital		(1909)	New York
University and Bellevue Hospital Medical College		(1912)*	New York
University of Buffalo School of Medicine		(1934)*	New York
University of Cincinnati College of Medicine		(1938)*	Ohio
University of Tennessee College of Medicine		(1929)*	Tennessee
Medical College of Virginia		(1930)	N. B. M. Ex.
Marquette University School of Medicine		(1938)	New York
University of Toronto Faculty of Medicine		(1936)	Illinois
McGill University Faculty of Medicine		(1935)*	Penna., (1937)* Illinois

* License has not been issued.
† One examined in medicine, the other in medicine and surgery.

Idaho October Report

Mr. H. B. Whittlesey, director, Bureau of Occupational License, reports the written examination for medical licensure held at Boise, Oct. 1-4, 1940. The examination covered 22 subjects and included 140 questions. An average of 75 per cent was required to pass. Eighteen candidates were examined, all of whom passed. The following schools were represented:

School	PASSED	Year Grad.	Per Cent
College of Medical Evangelists		(1940)	83
University of Colorado School of Medicine		(1938)	82
George Washington University School of Medicine		(1937)	85
Northwestern University Medical School		(1933)	82, 83, (1940) 83, 83
Rush Medical College		(1939)	83, 85
University of Illinois College of Medicine		(1930)	81
State University of Iowa College of Medicine		(1939)	84
St. Louis University School of Medicine		(1939)	84
Creighton University School of Medicine		(1936)	83
University of Nebraska College of Medicine		(1938)	83
Western Reserve University School of Medicine		(1938)	84
Temple University School of Medicine		(1939)	82
Baylor University College of Medicine		(1939)	82
Regia Università degli Studi di Bologna. Facoltà di Medicina e Chirurgia		(1937)	80

New Mexico October Report

Dr. Le Grand Ward, secretary, New Mexico Board of Medical Examiners, reports the written examination for medical licensure held at Santa Fe, Oct. 14-15, 1940. The examination covered 10 subjects and included 100 questions. An average of 70 per cent was required to pass. One candidate was examined and failed. Thirty-two physicians were successful in the examination held for endorsement applicants. The following schools were represented:

School	FAILED	Year Grad.	Number Failed
Universidad Nacional Facultad de Medicina, México		(1937)	1

School	PASSED	Year Grad.	Endorsement of
College of Medical Evangelists		(1934)*	Wisconsin, (1939) N. B. M. Ex.
University of Colorado School of Medicine		(1920)	Colorado
Yale University School of Medicine		(1931)	Louisiana
Chicago College of Medicine and Surgery		(1914)*	Illinois
Chicago Medical School		(1940)	Illinois
Loyola University School of Medicine		(1931)	Illinois
University of Illinois College of Medicine		(1939)	Texas
Drake University College of Medicine		(1913)	Iowa
State University of Iowa College of Medicine		(1916)*	Iowa
University of Kansas School of Medicine		(1936)	Kansas
Kentucky School of Medicine		(1905)	Oklahoma
Louisiana State University School of Medicine		(1936)	Louisiana, (1939)* Texas
Tulane University of Louisiana School of Medicine		(1932)	Louisiana
Boston University School of Medicine		(1929)	N. B. M. Ex.
Kansas City University of Physicians and Surgeons, Kansas City, Missouri		(1927)	Colorado
Washington University School of Medicine		(1939)	Missouri
University of Nebraska College of Medicine		(1918)*, (1936)	Nebraska
Long Island College Hospital		(1918)	New York
Long Island College of Medicine		(1931)	New York
New York Homeopathic Medical College and Flower Hospital		(1918)*	New York
University of Rochester School of Medicine and Dentistry		(1934) New York, (1938)	Ohio

University of Oregon Medical School	(1935)	Minnesota
Jefferson Medical College of Philadelphia	(1894)	Nebraska
University of Tennessee College of Medicine	(1939)	Texas
Baylor University College of Medicine	(1935), (1936), (1939)	Texas
Universität Bern Medizinische Fakultät	(1937)	Mass.

* Licenses have not been issued.

Connecticut Homeopathic November Report

Dr. Joseph H. Evans, secretary, Connecticut Homeopathic Medical Examining Board, reports the written examination for medical licensure held at Derby, Nov. 12-13, 1940. The examination covered seven subjects and included 70 questions. An average of 75 per cent was required to pass. One candidate was examined and passed. The following school was represented:

School	PASSED	Year Grad.	Per Cent
Hahnemann Med. College and Hospital of Philadelphia		(1940)	78.5*

One physician was successful in the oral examination held for endorsement applicants at Bridgeport, October 15. The following school was represented:

School	PASSED	Year Grad.	Endorsement of
New York Homeopathic Medical College and Flower Hospital		(1930)*	Indiana

* License has not been issued.

Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Medical Practice Act (Texas): Only Holders of Unlimited Licenses Eligible for Reciprocity.—The Texas medical practice act requires all applicants for licenses to practice medicine, regardless of their school of practice, to possess substantially equivalent educational qualifications as to years of study and to pass identical examinations in twelve subjects named in the act. Successful applicants are then licensed to practice medicine and surgery without restriction. An applicant who possesses a license to practice medicine and surgery without restriction issued by a state having standards equal to the standards required by the Texas medical practice act may be licensed by reciprocity and without examination (Vernon's Ann. Civ. St., Art. 4500, as amended, Laws, 1939, p. 352).

The appellants, twelve osteopaths not residents of Texas, possessed Missouri licenses permitting them to practice osteopathy alone and to use drugs only to a very limited extent. They instituted proceedings to compel the State Board of Medical Examiners of Texas to issue them licenses by reciprocity. The trial court entered a judgment for the board and the osteopaths appealed to the court of civil appeals of Texas, Austin.

The osteopaths admitted on appeal that they were not entitled to licenses by reciprocity but they contended that the Texas board had issued licenses by reciprocity to nonsectarian physicians possessing licenses to practice medicine and surgery in Missouri, and that the Missouri medical practice act did not impose standards equal to those imposed by the Texas act in that the Missouri act requires applicants to submit to examinations in only seven subjects while the Texas act requires examinations in twelve subjects. This, the osteopaths contended, constituted a discrimination against them in violation of Article 16, Section 31, of the Texas Constitution which provides that the legislature may pass laws prescribing the qualifications of practitioners of medicine in the state "but no preference shall ever be given by law to any schools of medicine." Since the osteopaths, said the court of civil appeals, have admitted that they have no right to a license by reciprocity, we do not know on what theory they have any right to maintain proceedings of this sort. Manifestly, the decision by this court as to licentiates of the Missouri "allopathic" school who have been issued licenses by reciprocity by the Texas board cannot bind such licentiates because they are not parties; and neither the osteopaths nor this court have any right to require or has entered a declaratory judgment affecting future applicants for licenses by reciprocity.

The osteopaths argued that the effect of the board's action when it licensed by reciprocity "Missouri allopaths" and refused such licensure to Missouri osteopaths amounted to a violation of the constitutional provisions referred to, in that such action was tantamount to saying that if an applicant possesses a license to practice osteopathy only in Missouri he cannot receive by reciprocity a license to practice osteopathy in Texas, thus making the osteopath's right to a license by reciprocity dependent on whether or not he could practice any and all of the healing arts. The Texas legislature, answered the court, in accordance with the constitutional mandate has provided for examinations relating to all who desire to practice medicine, which examinations are the same with respect to all schools of medicine, and such requirements do not prefer any school of medicine in contravention of the constitution, because they apply to all persons alike. The Texas statutes simply define a "practitioner of medicine" and require him to pass certain examinations touching his qualifications before he may obtain a license to practice any art of healing. When so licensed he may practice all of the arts of healing, without regard to any school of medicine to which he may belong. Manifestly, he cannot contend that, because he belongs to a certain school of medicine or does not desire to practice all of the arts of healing, he may take only such examinations as he may think will qualify him to practice one school of medicine or one art of healing. Nor does the fact that the statutes in question do not prohibit him to do so render them repugnant to the constitutional inhibition against the preferment of any one or more schools of medicine. The state constitution and statutes are not concerned with any particular school of medicine. They apply to all schools of medicine and to all persons alike, in that they provide that all who desire to practice medicine shall pass certain examinations relating to their qualifications, which entitles them to practice any one or all of the arts of healing. Nor does the fact that the defendant board has granted reciprocity licenses to some "Missouri allopaths" without examination discriminate against the appellants. These osteopaths do not possess the statutory requirements for a statutory reciprocity license and, having no right in the matter, they cannot complain of the action of the board as to others who possess other qualifications different from their own. The subjects of examination required of "Missouri allopaths" are not the same as those required of the Missouri osteopaths. And, suffice it to say, while Missouri allopaths are required to take examinations in only seven subjects, they are issued a license by the state of Missouri to practice medicine in all its phases, the same as the Texas license authorizes its practitioners to practice medicine in all its phases, although the Texas practitioner is required to be examined in twelve subjects. Whether the seven subjects in which the "Missouri allopaths" are required to be examined substantially cover the twelve subjects in which Texas practitioners of medicine are required to be examined is a matter within the jurisdiction of the defendant board; and there was no proof whatever that this was not true in the instant case.

Accordingly, the court of civil appeals affirmed the judgment of the trial court refusing to require the Texas board of medical examiners to license the osteopaths without examination.—*Ashby et al. v. Board of Medical Examiners of Texas, 142 S. W. (2d) 371 (Texas, 1940).*

Society Proceedings

COMING MEETINGS

Annual Congress on Medical Education and Licensure, Chicago, Feb. 17-18. Dr. W. D. Cutter, 535 North Dearborn St., Chicago, Secretary.

American Orthopsychiatric Association, New York, Feb. 20-22. Dr. Norvelle C. La Mar, 149 East 73d Street, New York, Secretary.

Central Surgical Association, Ann Arbor, Mich., Feb. 28-March 1. Dr. George M. Curtis, Ohio State University, Columbus, Ohio, Secretary.

Mid-South Post-Graduate Medical Assembly, Memphis, Tenn., Feb. 11-14. Dr. A. F. Cooper, Goodwyn Institute Bldg., Memphis, Tenn., Secretary.

Pacific Coast Surgical Association, Los Angeles, Feb. 19-22. Dr. H. Glenn Bell, University of California Hospital, San Francisco, Secretary.

Society of University Surgeons, St. Louis, Feb. 14-15. Dr. Frank Glenn, 525 East 68th St., New York, Secretary.

Current Medical Literature

AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1930 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

American Journal of Pathology, Boston

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Congenital Defects in Diaphragm. A. A. Liebow, Meriden, Conn., and H. C. Miller, New Haven, Conn.—p. 707.

Cytology of Fox Encephalitis and Effects of Centrifugation on Intranuclear Inclusions. A. M. Lucas, Ames, Iowa.—p. 739.

Etiology of Calcified Nodular Aortic Stenosis. E. M. Hall and T. Ichioka, Los Angeles.—p. 761.

Studies on Involution of Fetal Cortex of Adrenal Glands. Miriam C. Benner, Denver.—p. 787.

Response of Central Nervous System to Application of Carcinogenic Hydrocarbons: II. Methylcholanthrene. J. H. Peers, Columbia, Mo. —p. 799.

Pathology and Pathogenesis of Mammary Tumors Occurring Spontaneously in Albany Strain of Rats. A. W. Wright, G. H. Klinck Jr. and J. M. Wolfe, Albany, N. Y.—p. 817.

Primary Reticulum Cell Sarcoma of Spine: Report of Case with Autopsy. J. E. Edwards, Boston.—p. 835.

Comparative Experimental Studies of 200 Kilovolt and 1,000 Kilovolt Roentgen Rays: II. Biologic Effects on Bone Marrow of Albino Rat. J. R. Lingley, E. A. Gall and J. A. Hilcken, Boston.—p. 845.

American Journal of Psychiatry, New York

97:513-752 (Nov.) 1940. **Partial Index**

Direct Measurement of Nervous and Muscular States with Integrating Neurovoltmeter (Action Potential-Integrator). E. Jacobson, Chicago. —p. 513.

Quantitative Sex Hormone Studies in Homosexuality, Childhood and Various Neuropsychiatric Disturbances. R. Neustadt and A. Myerson, Boston.—p. 524.

Oxygen Consumption in Psychoses of Senium. D. E. Cameron, H. E. Himwich, S. R. Rosen and J. Fazekas, Albany, N. Y.—p. 566.

Clinical Significance of Bisulfite Binding Substances (B. B. S.) in Blood and Cerebrospinal Fluid. H. Wortis, E. Bueding and W. E. Wilson, New York.—p. 573.

*Treatment of Parkinsonian Syndrome with Bulgarian Belladonna Root and Amphetamine (Benzedrine) Sulfate. E. Davidoff, E. C. Reifenstein Jr. and N. R. Chambers, Syracuse, N. Y.—p. 589.

Histamine in Treatment of Psychosis: Psychiatric and Objective Psychologic Study. R. W. Robb, B. Kovitz and D. Rapaport, Osawatomie, Kan.—p. 601.

Migraine Equivalents. D. Slight, Chicago, and D. A. R. Morrison, Oconomowoc, Wis.—p. 623.

Study of Problem of Malnutrition in Institutionalized Psychotic Patients. H. C. Sharp and C. N. Baganz, Lyons, N. J.—p. 650.

Ideas of Contamination as Defense Against Sexuality. G. S. Sprague, White Plains, N. Y.—p. 659.

Nitrous Oxide Anoxia in Treatment of Schizophrenia: Report of Twenty-Four Cases. E. J. Fogel and L. P. Gray, Warren, Pa.—p. 677.

Further Experiences with Picrotoxin as Convulsant in Treatment of Mental Illnesses: Method of Combining Picrotoxin with Metrazol. A. A. Low, Elizabeth MacDougall, E. Ross, M. Sachs and D. Levitin, Chicago.—p. 686.

Masculinity and Femininity in Psychotic Patients, as Measured by Terman-Miles Interest-Attitude Analysis Test. Beulah Bosselman, Chicago, and B. Skorodin, Manteno, Ill.—p. 699.

Treatment of Morbid Sex Craving with Aid of Testosterone Propionate. H. S. Rubinstein, Baltimore; H. D. Shapiro and W. Freeman, Washington, D. C.—p. 703.

Bulgarian Belladonna and Amphetamine Sulfate for Parkinsonian Syndrome.—Davidoff and his collaborators used rabellon (a synthetic combination containing the same concentration of alkaloid as the most effective extracts of Bulgarian belladonna root) in combination with amphetamine sulfate for the treatment of 15 patients with postencephalitic and 10 with arteriosclerotic or idiopathic parkinsonism. Many of these patients had been subjected to various other therapies. Seven of the 10 patients with the postencephalitic type of the disorder were psychotic and only 1 with the arteriosclerotic type was thought to have a psychosis. The procedure for administering rabellon depends on establishing the optimal dose for the individual patient. This is done by increasing daily the dose of a fourth of a tablet once a day to a fourth three times a day and then to half a tablet three times a day and so on. The patient is instructed to eliminate all alcohol, coffee and nicotine and to avoid meats, particularly spiced meats. When the minimal dosage that produces the optimal effect is established it is maintained thereafter. For patients who tolerate the drug poorly the dosage is not increased as rapidly. The appearance of mild toxic manifestations in these patients may be of value in indicating that the optimal dosage has been exceeded. After the patients had been maintained on a stable program of rabellon medication for several weeks, amphetamine sulfate medication was begun. The initial dose was 5 mg. in the morning and at noon. The dosage was increased at weekly intervals by increments of 5 mg. until the maximal of from 30 to 40 mg. was reached. The optimal dosage for many patients was 15 to 20 mg. daily. The dose of rabellon was decreased as the dose of amphetamine was increased. On the combination therapy 8 of the 15 patients with postencephalitic parkinsonism exhibited marked improvement, 3 moderate improvement and 4 no benefit; that is to say, 7 of the 8 without psychosis and 4 of the 7 with psychosis were favorably influenced by the therapy. Of the 10 with idiopathic and arteriosclerotic parkinsonism, 5 showed considerable improvement and 5 were unimproved. The patient with idiopathic parkinsonism with psychotic manifestations showed temporary amelioration but relapsed and was classified as unimproved. The results show that the combined therapy is superior to other forms of treatment.

American Journal of Public Health, New York

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Improved Management of Gangrene of Foot. W. F. Bowers and J. C. Kennedy, Omaha.—p. 573.

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Early Diagnosis of Cancer. I. I. Kaplan, New York.—p. 781.

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*Mucous Colitis: Delineation of Syndrome with Certain Observations on Its Mechanism and on Role of Emotional Tension as Precipitating Factor. B. V. White and C. M. Jones, Boston.—p. 854.
*Tuberculosis Among Students and Graduates in Nursing. J. A. Myers, Ruth E. Boynton, H. S. Diehl, T. L. Streukens, Minneapolis, and P. T. Y. Ch'Iu, Peiping, China.—p. 873.
Arterial Oxygen Saturation in Cirrhosis of Liver. R. C. Darling, New York.—p. 898.
Study of Acute Leukoses. J. Kaufmann and L. Lowenstein, Montreal, Canada.—p. 903.

Blood Sedimentation Test as Routine Diagnostic Procedure.—Agnor evaluates the sedimentation test from a study of the records of 2,063 patients with all types of disease. The test was performed as a routine procedure by a modification of the Westergren method. The one hour determination was considered to be the significant value, and a rate of more than 20 mm. was considered abnormal. The study indicates that the sedimentation rate is important enough to be employed as routine, as are blood counts and urinalyses in some diseases and serologic tests for syphilis. In the present series 176 cases, 8.5 per cent, showed changes in the serologic reactions of the blood. Similarly, 331 cases, 16 per cent, with abnormal blood counts gave specific information leading to the detection of the particular disease. Also in 207 cases, 10 per cent, the urinalysis gave specific information leading to a diagnosis. Therefore in 34.5 per cent of the cases the generally employed routine diagnostic tests were of specific value. On the other hand 702 cases, 34.1 per cent, showed an increased sedimentation rate, which although not specifically yet definitely indicated disease. Further analysis shows that of 1,549 patients with definite organic disease 681, or 43.9 per cent, had elevated rates; of the 514 without such evidence only 4 per cent had elevated rates. Among the latter patients were 5 instances in which the sedimentation rate was more than 30 mm. in one hour and 16 in which it was between 21 and 30 mm. The records of these 21 patients were subjected to a careful study; among them there was only 1 man, and he was discharged as a case of unclassified psychosis. He gave a history of having been treated in a tuberculosis sanatorium for eighteen months a few years before. Examination of the chest and of the sputum was negative, but tuberculosis may have accounted for the rapid rate. Of the remaining 20 patients with elevated rates, 10 were obese and for the other 10 there is no apparent explanation. There is no apparent association of obesity and increased sedimentation rate, but the coincidence was observed. Certain organic diseases seldom produce an increase in the blood sedimentation rate. Other diseases (chronic and acute infections, malignant conditions, localized suppurations and tuberculosis) may have an increased rate. The 1,549 cases in which there was evidence of organic disease were subdivided into cases of diseases usually associated with an increased sedimentation rate and a group in which such evidence was lacking. There were 85 cases with elevated rates in which the organic disease present is usually associated with a normal sedimentation rate. These 85 and the 21 previously mentioned represent 106 cases, 5 per cent of the series, in which an increased sedimentation rate was misleading. Therefore a sedimentation rate of more than 20 mm. in one hour was indicative of an organic disease of a type usually associated with an increased sedimentation rate in 95 per cent of the cases. An increased sedimentation rate in males showing no evidence of disease was observed only once. In general an increased rate in the male was more likely to be present with a disease usually associated with an increased rate than in the female.

Pulmonary Emphysema.—In studying the heart and pulmonary arterial tree in 32 cases of essential emphysema, Parker found that emphysema enlarged the right ventricle in 75 per cent and caused heart failure with decompensation in 44 per cent of the entire group. The severity of emphysema seemed closely correlated with the incidence of congestive heart failure as well as the frequency and extent of right ventricular enlargement. Some arteriosclerosis of the pulmonary arterial tree was observed among 80 per cent of the cases. Arteriosclerotic changes were noticed most frequently in the arterioles, and narrowing of the arteriolar bed was found in 66 per cent of the cases studied. The degree of obliteration of the arteriolar bed seemed influenced by the severity of the emphysema, yet there was no direct correlation between the degree of arteriolar sclerosis and that of the right ventricular enlargement, nor any relationship between the extent of the pulmonary arteriolar changes and the arteriosclerotic changes in the coronary arteries or the aorta. Therefore the author concluded that the arteriosclerotic changes of the pulmonary vessels in emphysema represent secondary manifestations of an existent hypertension within the pulmonary circuit which probably is produced by obstruction in the capillary bed. Although it may be assumed that when the degree of obstruction in the arteriolar system is great there is an augmentation of the pulmonary hypertension, it is doubtful that the amount of pulmonary arteriosclerosis usually seen in emphysema produces alone a serious obstruction to the pulmonary circulation.

Mucous Colitis.—White and Jones made a thorough clinical study of 60 patients with mucous colitis with the view of obtaining a basis for statistical deductions. Fifty-seven of the patients were studied psychologically in order to determine the role of precipitating emotional factors and personality types of the victims. Symptoms and signs of mucous colitis are constipation or diarrhea, abdominal cramps aggravated during peristaltic stimulation, palpable and tender sigmoid colon and certain minimal mucosal changes in the rectosigmoid as observed through the sigmoidoscope. Abdominal pain was the only constant observation. Mucous colitis may exist without abdominal pain. The disease usually has its onset in early adult life. The average age of the 60 patients at the onset of symptoms was 23.4 years. At the time of the study their average age was 35.8 years, indicating a long prediagnostic period. In 38 instances the original diagnosis was other than "colitis." Constipation at some time in the course of the illness was complained of by 80 per cent, diarrhea by 47 per cent. The percentages of other significant clinical observations were: stools of small caliber, 95; palpable colon, 88; pain on defecation, 81; pain related to food ingestion, 71; mucoid stools, 58; tensional headache, 66; dermographia, 60; excess catharsis, 37, and needless surgery, 31. A number of conditioning factors seem to play a part in the production of its symptoms. Among them are direct irritants (rough foods, enemas, cathartics and infections of the colon), instability of the autonomic nervous system, general infectious diseases, sudden weight loss and physical "softness," specific food allergy and emotional tension. From the psychologic study of 57 patients the authors find that in most instances mucous colitis appears to be a somatic response to a type of nervous tension. Mental states conducive to this response appear to be anxiety, resentment and guilt. Associated depressive, neurasthenic and hypochondriac features are often present, but no one psychiatric diagnosis is predominant. A rigid type of thinking, similar to that seen in obsessive-compulsive states, is present in 50 per cent of the cases and may play a part in prolonging periods of tension. Symptoms of mucous colitis appear to represent a clear-cut somatic response to tension and not to be psychologically determined and obviously gainful, such as those seen in hysteria.

Tuberculosis in Nurses.—Myers and his colleagues present the observations begun in 1929 among student and graduate nurses in four schools on entrance and throughout their course of training, using college of education students as a control group. School 2 had no tuberculosis service and of 120 students under observation 18 were tuberculin reactors on entrance; 35 became reactors while in school, and 67 graduated as nonreactors. In 2 of the 18 who entered as reactors, pulmonary tuberculosis developed while in school; 1 of the 35 who later

reacted had a primary focus in the lung parenchyma demonstrated on roentgen examination. School 3 had no tuberculosis service, and here 204 students were observed; 50 were reactors on entrance, 43 became reactors while in school and 111 were graduated as nonreactors. In none of the reactors on entrance did demonstrable lesions develop while in school. Of those who became reactors, a primary focus in the lung demonstrable on the roentgenogram developed in 1 and bilateral clinical disease developed in 1 more than eighteen months after she was known to be a reactor. School 4 required a six weeks tuberculosis service of each student. Of 550 observed, 165 reacted on entrance, 204 became reactors while in school and 181 graduated as nonreactors. Of the 165 who entered as reactors, demonstrable lesions developed in 4 while in school and in 2 after graduation. Of the 204 who became reactors as students, lesions demonstrable on roentgen study or otherwise developed in 19 while in school and in 5 after graduation. In school 1 there was a twelve weeks tuberculosis service during the first part of the study, and of the 226 students observed 48 reacted on entrance, 137 became reactors while in school and 41 graduated as nonreactors. Of the reactors on entrance, lesions demonstrable on roentgen study or otherwise developed in 2 while in school or after graduation. Of those who became reactors, demonstrable lesions developed in 14 in school or after graduation. A questionnaire to schools 2, 3 and 4 in 1938 revealed that some of the nonreactors on graduation had since become infected and lesions demonstrable on roentgen study or by other methods had developed in a few. The authors believe that every reactor to tuberculin has one or more primary tuberculosis complexes in the body. In their group the number in whom lesions demonstrable on roentgen or other study have developed or who have become ill from tuberculosis is sufficiently large to make the problem a serious one. Of the students entering the college of education 24.8 per cent reacted to tuberculin, whereas on graduation 28.5 per cent reacted. Lesions which were demonstrated on roentgen examination developed in school in only 3 of 686 reactors. Obviously, the increase in the percentage of reactors depends on contact with contagious cases of tuberculosis. Throughout the study tuberculosis did not develop in a nonreactor to tuberculin. Their observation period is short for such a chronic disease, and therefore the authors think that more of the former students will fall ill from tuberculosis, especially as new cases have been reported annually. They do not believe that BCG has been proved sufficiently efficacious to solve the problem, as there is evidence of tuberculosis among some of the students so treated. In their opinion only a most rigid contagious disease technic provides a barrier and prevents the spread of tubercle bacilli from patient to student.

Archives of Internal Medicine, Chicago

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*Comparison of Sulfathiazole and Sulfapyridine in Treatment of Pneumococcic Pneumonia. C. F. Garvin, Cleveland.—p. 1246.
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Pneumococcic Pneumonia: Analysis of Records of 1,469 Patients Treated in Los Angeles County Hospital from 1934 Through 1938: I. Character of Pneumonia Caused by Various Types of Pneumococci; Complications; Outcome of Pneumonia in Presence of Certain Variations in the Patient and in the Course of the Disease. F. J. Moore, R. E. Thomas, M. Kistler, R. M. Ireland and V. E. Hallstone, Los Angeles.—p. 1290.
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*Multiple Primary Malignant Lesions of Large Bowel. L. R. Schweiger and J. A. Bargen, Rochester, Minn.—p. 1331.
Review of Neuropsychiatry for 1940. S. Cobb, Boston.—p. 1341.

Sulfathiazole and Sulfapyridine for Pneumonia.—Garvin compares the results of sulfathiazole and sulfapyridine in the treatment of pneumococcic pneumonia; 40 patients were treated with sulfathiazole and 62 with sulfapyridine. Five extremely ill patients of the first and 13 of the second group also received specific antipneumococcus serum. Five of the 40 patients treated with sulfathiazole died, as did 11 of those treated with sulfapyridine. Exclusive of the patients moribund on admission and who died within twenty-four hours, the corrected respective mortality is 10.3 and 8.9 per cent. The average age of the patients treated with sulfathiazole was 38.1 and of those treated with sulfapyridine 44.8 years. Treatment was begun in three and six-tenths days after the onset of the disease in the first group and in four and four-tenths days in the second group. An average of one and six-tenths lobes was involved among the patients receiving sulfathiazole and one and five-tenths lobes among those receiving sulfapyridine. There was no statistical difference between the two groups as to sex and color. There was a normal temperature within twenty-four hours among 14.3 per cent of the patients given sulfathiazole and of an additional 14.3 per cent within forty-eight hours and of an additional 20 per cent within seventy-two hours. The respective figures for the other group were 13.7, 33.3 and 5.9 per cent. After the temperature had once reached normal, 71.4 and 78.4 per cent of the two respective groups of pateints had a secondary rise above 99.5 F. In the majority of instances this was of no consequence. The average number of hospital days for the two groups was seventeen and four-tenths days. Two patients of the group treated with sulfathiazole had pleural effusion, 1 empyema, 1 slow resolution and 2 pulmonary abscess. Among the group treated with sulfapyridine, empyema occurred in 4, slow resolution in 1 and pulmonary abscess in 2. Sulfathiazole caused less vomiting but more crystals (61.5 as compared to 28.6 per cent) in the urine than did sulfapyridine. Otherwise toxic manifestations were not significantly different. Approximately twice as much sulfathiazole as sulfapyrinine was required to maintain an average concentration of from 5 to 6 mg. of the free drug per hundred cubic centimeters of blood.

Acacia for Nephrotic Edema.—Goudsmit and Binger find that acacia can be incorporated advantageously into the regimen (salt-free, high protein diet, fluid restriction and diuretic salts) of the patient with nephrotic edema. Of 40 successive adult patients treated according to these principles, all but 4 were promptly relieved of edema. Failure of the treatment was usually due to the fact that the patient was unable to take sufficient nourishment and diuretic salts by mouth. Diuretic salts are not essential, as acacia may produce diuresis when used in conjunction with the diet. However, the best results are obtained if diuretic salts are included. Except in a few instances, mercurial diuretics can be dispensed with without sacrificing therapeutic results. Sometimes diuretics that are ineffective before treatment with acacia become effective after such treatment. Reactions after injection of acacia are infrequent and mild if care in preparation and administration is taken. The dosage in each course of treatment should be limited to from 90 to 150 Gm. divided in daily doses of 30 Gm. The acacia was usually administered as a 6 per cent solution in distilled water. Usually 500 cc. of the solution was given in one day. From forty-five to seventy-five minutes was allowed for its administration. It was given every day or on alternate days, whichever was tolerated better. As hepatic enlargement has not been observed, acacia may even be given to patients who have cirrhosis of the liver without further impairing its function. The decrease in serum proteins after injection of acacia is accounted for adequately on the basis of increase in plasma volume and concomitant dilution of its constituents. Renal insufficiency, secondary vascular disease or myocardial degeneration does not contraindicate its use. Its addition to the general regimen provides efficient results for the patient with nephrotic edema.

Multiple Primary Malignant Intestinal Lesions.—Since the report of Rankin and Bargen in 1930, Schweiger and Bargen collected from the records of the Mayo Clinic 23 cases of multiple primary malignant lesions of the large intestine. They divide them into two groups: those in which multiple cancers occur simultaneously (synchronous) and those which occur at different times (metachronous). Instances of multiple polyps of low malignant grades and single grossly carcinomatous lesions that were associated with single polyps of low malignant grade

were excluded. The possibility of implantation or extension from one lesion to another was precluded. The authors believe that many instances of multiple independent lesions in the intestine are probably not recognized. It is important to the patient that the physician exclude the possibility of other lesions, as some poor results after operation for cancer may be attributable to synchronous or metachronous lesions, unsuspected and therefore undiscovered. Curability by operative means will improve only as thorough diagnoses are made earlier. Only when a diagnosis of hemorrhoids is made after all other possible causes of intestinal bleeding have been excluded will the percentage of inoperable cases of cancer of the large intestine diminish. Once a patient has become the victim of such a malignant lesion he should watch for warning signs of recurring trouble. Many patients after having had a cancer of the colon removed assume erroneously that from that time forth they are immune to a similar morbid process. The pathogenesis of polyps may also explain the origin of cancer of the colon. Polyps play a role in the genesis of some cancers. The importance of a careful examination of the entire large intestine when cancer is found at any point is emphasized.

Archives of Otolaryngology, Chicago

32:1007-1138 (Dec.) 1940

Pneumococcic Meningitis: Review of the English Literature: Report of Two Cases in Which Disease Was of Otitic Origin. G. B. Gilmore and P. Sacks, New York.—p. 1007.
Primary Malignant Tumors of Temporal Bone: Report of Case. H. B. Stokes, Omaha.—p. 1023.
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Psychology of Laryngeal Functions. E. Froeschels, New York.—p. 1039.
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Objective Tinnitus Aurium: Report of Case. J. C. Donnelly, Philadelphia.—p. 1054.
Angioneurotic Edema of Larynx Due to Sensitivity to Chicle: Report of Case. D. I. Frank, New York.—p. 1067.

Endocrinology, Los Angeles

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Abnormal Growth in Strain of Rats Characterized by Low Fertility and High Incidence of Benign Mammary Tumors. J. M. Wolfe, Ethel Burack and A. W. Wright, Albany, N. Y.—p. 883.
Evidence for Presence of Second Mammogenic (Lobule-Alveolar) Factor in Anterior Pituitary. J. P. Mixner, A. A. Lewis and C. W. Turner, Columbia, Mo.—p. 888.
Studies on Relationship of Sex Hormones to Infection: IV. Study of Dispersion or Concentration of India Ink in Skin by Certain Sex Hormones. D. H. Sprunt and Sara McDearman, Durham, N. C.—p. 893.
Effect of Diethyl Stilbestrol Dipropionate on Endometrial Transplants. B. B. Weinstein, J. C. Weed, C. G. Collins, F. R. Lock and J. V. Schlosser, New Orleans.—p. 903.
Difference in Action on Heart Beat Compared with That on Metabolism of Normal and Toxic Goiter Thyroids. A. E. Meyer and M. M. Thompson, Brooklyn.—p. 917.
Further Studies on Ovarian-Thyroid Relationship. T. C. Sherwood, Madison, Wis.—p. 925.
Hypophysis and Hemopoiesis. O. O. Meyer, Ethel W. Thewlis and H. P. Rusch, Madison, Wis.—p. 932.
Effect of Adrenal Cortex on Carbohydrate Metabolism. R. A. Lewis, D. Kuhlman, C. Delbue, G. F. Koepf and G. W. Thorn, Baltimore.—p. 971.
Atrophy of Adrenal Cortex Following Administration of Large Amounts of Progesterone. H. J. Clausen, Denver.—p. 989.

Vaginal Smear and Functional Sterility.—Rubenstein describes eight types of epithelial cells which most accurately reflect the gonadal hormone production in vaginal smears. The vaginal mucosa of children, old women and certain amenorrheic adult women is very thin and consists of basal layers of cells. These cells are characteristically round, somewhat larger than the large mononuclear leukocytes. In the nonpregnant woman they usually show various degrees of cornification. In the event of pregnancy the corpus luteum increases, and increasing amounts of theelin and progesterone are produced, in response to which cell types appear which may be used to diagnose pregnancy. Study of typical smears at various phases of the menstrual cycle shows that anovulatory cycles occur more frequently than heretofore supposed. The presence of infection or chronic irritation may invalidate the interpretation of vaginal smears and temperatures. Usually the vaginal smear and basal rectal temperature will show a discrepancy when some nongonadal influence affects one or the other; thus the combination of the two methods makes the other more reliable. The correlation between the temperature and gonad function is as follows: During the phase of follicle development and increasing theelin production, the basal rectal temperature drops progressively. The low point is reached just before ovulation, when conception is most likely. The temperature rise continues after ovulation and should exceed 0.5 F. in the first twenty-four hours and 1 F. the first week. As soon as the corpus luteum has regressed (a few days premenstrually) new follicles begin to develop. Theelin production begins again, although at a low level. Since there is now no functional corpus luteum, the temperature depressing action of theelin is again apparent. The temperature drops progressively throughout the premenstrual phase of the cycle. In the event of pregnancy, corpus luteum function persists and the postovulative temperature rise is maintained. If temperature curves of previous cycles are available it is sometimes possible to detect a pregnancy before the period is missed, as the temperature remains high. The temperature and smear technics used together have proved to be as reliable in detecting early pregnancy as the Friedman test. By use of the smear-temperature technic it has been possible to classify three varieties of functional sterility. The commonest type of functional sterility is that in which the cycles are anovulatory, in which smears show marked desquamation characteristic of ovulation with no clear-cut and sudden rise in temperature. Instead the temperature rises gradually. In the amenorrheic anovulatory cycle there is no rise in temperature and the smears persistently show typical cells. A study of 739 cycles of 101 patients (66 of whom complained of sterility) showed that 338 seemed anovulatory; no patient was exempt from at least a single anovulatory cycle. Other causes of functional sterility are early abortion, failure of implantation and ovulation when coitus is avoided. In investigating functional sterility, attempts to determine the time of ovulation and any hormone deficiency in the preovulative or postovulative phase of the cycle and attempts to influence the cycle by appropriate therapy controlled by the vaginal smear-basal body temperature technic are indicated. If ovulation occurs, coitus is advised on the preovulative and ovulative days. If ovulation does not occur, therapy is directed to induce it. If the sterility is due to a deficiency in the corpus luteum phase of the cycle, luteinizing hormone or progesterone is indicated.

Illinois Medical Journal, Chicago

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New Artificial Larynx with Historical Review. W. L. Hanson, East St. Louis.—p. 483.
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Splenic Extract in Glaucoma: Preliminary Report. M. Goldenburg, Chicago.—p. 495.
Stomach Diverticulum: Case Report. E. H. Warszewski and H. A. Jacobson, Chicago.—p. 500.
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Johns Hopkins Hospital Bulletin, Baltimore

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Hyperplastic Mammary Nodules in Castrate Female Rhesus Monkey. H. Speert, Baltimore.—p. 414.

Toxicity, Absorption and Chemotherapeutic Activity of 2-Sulfanilamidopyrimidine (Sulfadiazine). W. H. Feinstone, R. D. Williams, R. T. Wolff, Evelyn Huntington and M. L. Crossley, Stamford, Conn.—p. 427.

March Hemoglobinuria: Case Report. A. M. Fisher and A. Bernstein, Baltimore.—p. 457.

Journal of Bacteriology, Baltimore

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Culture Mediums for Brucella. Grace P. Kerby and R. M. Calder, Houston, Texas.—p. 637.

Nutritional Requirements of Pneumococcus: I. Growth Factors for Types I, II, V, VII, VIII. L. Rane and Y. Subbarow, Boston.—p. 695.

Activity of Chemotherapeutic Agents. R. L. Libby, Pearl River, N. Y.—p. 733.

Journal of Lab. and Clinical Medicine, St. Louis

26:443-596 (Dec.) 1940

Critical Histopathologic Study: Fifty Postmortem Patients with Cancer Subjected to Local or Generalized Refrigeration Compared to Similar Control Group of Thirty-Seven Nonrefrigerated Patients. M. E. Sano and L. W. Smith, Philadelphia.—p. 443.

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Leukocyte Changes in Acute Peritoneal Irritation. R. E. Kaufman and F. von Saal, New York.—p. 468.

*Effect of Belladonna on Appetite of Patients with Obesity and with Other Diseases. J. A. Greene, Iowa City.—p. 477.

Toxic Effects of Sulfanilamide, Sulfapyridine and Rodilone in Anoxia. G. A. Emerson, D. W. Northup and E. J. Van Liere, Morgantown, W. Va.—p. 479.

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Observations on Interrelationship of Capillary, Platelet and Splenic Factors in Thrombocytopenic Purpura. R. H. E. Elliott Jr. and Mary A. Whipple, New York.—p. 489.

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Acid-Base Balance in Plasma and Blood Cells of Normal Nonpregnant, Pregnant and Puerperal Women. F. W. Oberst, Lexington, Ky., and E. D. Plass, Iowa City.—p. 513.

Magnesium Content of Blood Serum and Urine. M. Bernstein and S. Simkins, Philadelphia.—p. 521.

Influence of Glycerol on Glycemia in Normal and Diabetic Individuals. M. Wishnofsky, A. P. Kane, W. C. Spitz, S. Michalover and C. S. Byron, Brooklyn.—p. 526.

Guanidine-like Substances in Blood: VII. Guanidine and Other Blood Constituents in Experimental Anoxemia. J. E. Andes, E. J. Van Liere, Erlene J. Andes and P. Vaughn, Morgantown, W. Va.—p. 530.

Comparison of Chloride Concentrations in Whole Blood and Spinal Fluid. R. S. Hubbard and G. M. Beck, Buffalo.—p. 535.

Effect of Belladonna on Appetite.—Greene observed that hunger could be controlled by belladonna and bromide or phenobarbital. He gave such medication to 39 obese patients, 5 with diabetes and overweight and 1 with chronic pyelonephritis with overweight. The medication was given the patients without their knowledge of its purpose. The appetite of 40 of the 45 patients was diminished after medication. The medication was an important factor in reducing the appetite, as 10 patients who omitted the medication of their own accord resumed it because hunger returned. The effect of the drug appears to continue indefinitely as long as the medication is continued. One of the patients with diabetes and moderate obesity is of particular interest. She was never able to control the diabetes because hunger caused her to eat between meals. Tincture of belladonna, 10 drops three times a day, before meals, eliminated this hunger and permitted the control of the diabetes. The patient with the pyelonephritis was forced to limit her activity because of the nephritis and hypertension, she began to gain weight and the administration of tincture of belladonna decreased her food intake sufficiently to stop the gain in body weight. Omission of the drug at a later date was followed by gain in body weight, and reduction again followed the administration of the drug. The cause of the increase in appetite of patients with obesity is not known. Harrington and Newburgh have stated that many patients ingested food at frequent intervals because of nervousness or of habit. The author's observations support this contention and for this reason a mild sedative is of distinct aid in controlling the appetite of such patients. The fact that belladonna decreases appetite suggested that an alteration of the motility of the stomach or small intestine may be a contributing cause.

Journal of Urology, Baltimore

44:545-726 (Nov.) 1940

Physical Factors Influencing the Growth of Cancer (Experimental Studies Based on Renal Adenocarcinoma in Animals). B. Lucké, Philadelphia.—p. 545.

*Chronic Bilateral Pyelonephritis and Hypertension. W. F. Braasch and C. E. Jacobson, Rochester, Minn.—p. 571.

*Papillary Pathology as Precursor of Primary Renal Calculus. A. Randall, Philadelphia.—p. 580.

Prevalence and Importance of Urea-Splitting Bacterial Infections of Urinary Tract in Formation of Calculi. R. Chute and H. I. Suby, Boston.—p. 590.

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Role of Perirenal Insufflation in Urology. L. F. Ajamil, J. G. Romeu, J. M. Vega and J. L. Montejo, Habana, Cuba.—p. 607.

Perirenal Air Insufflation: Aid in Urologic Diagnosis. R. A. Burhans, Lansing, Mich.—p. 618.

Leukoplakia of Urinary Bladder: Report of Thirty-Four Clinical Cases. G. J. Thompson and J. J. Stein, Rochester, Minn.—p. 639.

Subtotal Cystectomy in Treatment of Hunner Ulcer. A. I. Folsom, H. A. O'Brien and G. T. Caldwell, Dallas, Texas.—p. 650.

Effect of Trasentin and Morphine on Urinary Bladder of Unanesthetized Dog. R. E. Van Duzen, D. Slaughter and I. C. Winter, Dallas, Texas.—p. 667.

Pharmacology in Vitro of Human Vasa Deferentia and Epididymis: Question of Endocrine Control of Motility of Male Accessory Genitals. T. Martins, J. R. Valle and A. Porto, São Paulo, Brazil.—p. 682.

Effect of *p*H on Growth of Bacteria in Urine. R. C. Yeaw, New York.—p. 699.

Use of Sulfathiazole Before and After Urologic Operations to Prevent or Combat Infection. H. H. Young, Justina H. Hill and J. H. Semans, Baltimore.—p. 714.

Chronic Bilateral Pyelonephritis and Hypertension.—Braasch and Jacobson examined 180 patients with chronic bilateral pyelonephritis to ascertain the possible role of chronic renal infection or its associated pathologic changes on the production of hypertension. The patients were subjected to a cystoscopic examination during which pyuria from both kidneys was revealed. Urographic data of 77 per cent of the patients were available and in all of them changes in the ureter, the pelvis or calices were demonstrable. Hypertension was considered present if the systolic blood pressure exceeded 145 mm. or the diastolic 90 mm. of mercury. Values for blood urea above 40 mg. per hundred cubic centimeters were considered above normal. Hypertension was present among 47, or 26.1 per cent, of the patients. This was an increase of 6 per cent over that found among a random control group. The increase was particularly prominent among patients less than 50 years of age; the incidence was almost twice that of the control group. The incidence among patients 50 or more years of age was approximately the same for the two groups. In identical age groups the incidence of hypertension was higher among those with pyelonephritis than that of the control group. An apparent relation existed between the incidence of hypertension and the duration of symptoms of pyelonephritis; the incidence usually increased with the duration of symptoms. However, the blood pressure of some patients remained normal after a history of pyelonephritis for from fifteen to twenty years. The highest incidence of a relation between the degree of pathologic change in the kidneys and ureters, as evidenced by the degree of deformity in the urogram and the incidence of hypertension, was evidenced by patients among whom the pathologic changes were most marked. Impaired renal function does not necessarily imply hypertension, as the blood pressure was normal among more than half of such patients. However, hypertension was found twice as often with impaired renal function as with normal renal function. Approximately 75 per cent of the patients with hypertension had a systolic blood pressure of less than 180 mm. of mercury and only 4 a systolic blood pressure of more than 200 mm. Thus the hypertension of these patients is usually of a comparatively benign nature. The usual micro-

organisms of the urinary tract were found. Among patients affected with Aerobacter aerogenes the incidence of hypertension was 38.5 per cent; this may be significant. The hypertension occasionally observed in mild or recurrent chronic pyelonephritis in which renal function is normal but no urographic deformity exists appears to be of independent origin and may be termed "essential hypertension."

Papillary Abnormality as Precursor of Renal Calculus.—Randall presents evidence to prove that three common urinary salts (phosphates, oxalates and uric acid) crystallize into primary renal calculi on a common, simple pathologic entity. By "primary renal calculus" is meant a small renal stone wherein (by current investigative means) one recognizes nothing responsible for its origin: no stasis, infection, hypovitaminosis, hyperparathyroidism or hyperexcretory state. Urologic studies offer two facts which aid materially in reasoning into the cause of primary renal calculus. They are that a calculus is of slow growth and its characteristic location of origin is in a minor calix. These facts suggested to the author that renal calculus is essentially a symptom of some morbid pathologic change that, in its turn, was the precalculus or initiating lesion. In searching through 1,154 necropsies for such a lesion, the deposition of calcium salts in the renal papilla was revealed. This calcium salt deposit, when intrapapillary, is an inert replacement manifestation; but in its growth and if near the surface of the papillary wall it can lose its surface covering of epithelial cells through decubitus and then be bathed in caliceal urine. This is the nidus. This calcium plaque formation has been dissected out and calcium was present in the renal papilla in 19 per cent, nitrogen in 10 per cent and carbon dioxide in 1 per cent of the cases. Phosphorus was present but difficult to estimate accurately. A study of the incidence by decades and of 65 necropsy cases, also studied by decades, in which visible calculi up to 8 mm. in size were found adherent to a renal papilla, presents definite proof of the papillary origin of a primary renal calculus. The various salts which go to make different types of renal stone can so deposit and grow into a primary renal calculus. Calculi of differing salt compositions do have their origin from such pathologic changes in the renal papilla. Calculi supposed to be associated with hyperparathyroidism, hypovitaminosis, odd forms of renal infection, cases of nephrocalcinosis and so on belong to a separate and different form of papillary pathologic change associated with tubular inspissation of salts (calcium infarction) and represent the end results of hyperexcretory states.

Maine Medical Association Journal, Portland

31:315-338 (Dec.) 1940

Chemotherapeutic Procedures in Pneumococcic Meningitis: Fatal Case of Type XIX Pneumococcic Meningitis Treated with Sulfapyridine and Type Specific Rabbit Serum: Clinical and Postmortem Findings. C. W. Steele, J. Gottlieb and H. Brann, Lewiston.—p. 315.
Use of Intelligence Tests in Diagnosis of Psychotic Patients. Grace R. Foster, Augusta.—p. 321.
The Cross-Eyed Child—Some Important Considerations. L. H. Berrie, Houlton.—p. 325.

Medicine, Baltimore

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Mechanism of Hydrogen Transport in Animal Tissues. V. R. Potter, Madison, Wis.—p. 441.
Pathogenesis of Paroxysmal Pulmonary Edema. A. Luisada, Waltham, Mass.—p. 475.

Michigan State Medical Society Journal, Muskegon

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Seventy-Five Years of Social Contribution: Historical Review. B. R. Corbus, Grand Rapids.—p. 919.
Leukocyte Counts: Evaluation of Total, Differential and Absolute Counts. E. E. Osgood, Portland, Ore.—p. 924.
Bilateral Small Cell Carcinoma: Report of Case in Girl 15 Years Old. W. W. MacGregor and H. Small, Detroit.—p. 929.
Varicose Veins: Surgical Treatment of 100 Cases Analyzed. J. G. Slevin, Detroit.—p. 932.
Varicose Ulcers: Newer Methods of Treatment. H. C. Rees, Detroit.—p. 936.
The Eye in General Practice. E. L. Cooper, Detroit.—p. 939.
Nasal Polyposis. N. Bentley, Detroit.—p. 944.
Subacute Bacterial Endocarditis: Apparent Recovery. L. T. Colvin, Detroit.—p. 946.
Chorionepithelioma of Uterus, with Perforation and Intra-Abdominal Hemorrhage. M. R. White, Detroit.—p. 949.
Confusing Tuberculosis. C. E. Black, Lansing.—p. 952.

New England Journal of Medicine, Boston

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*Congenital Diaphragmatic Hernia. W. E. Ladd and R. E. Gross, Boston.—p. 917.
Indications for Gastroscopy. E. B. Benedict, Boston.—p. 925.
Pulmonary Infarction as Cause of Pneumothorax. J. H. Marks, Boston.—p. 934.
*Significance of Charcot-Leyden Crystals. J. H. Thompson and F. K. Paddock, Boston.—p. 936.
Arterial Hypertension. S. Weiss, Boston.—p. 939.

Congenital Diaphragmatic Hernia.—Ladd and Gross report 25 cases of congenital diaphragmatic hernia encountered at the Children's Hospital. The early policy was to delay operation until the child was older, and of 9 such patients 5 are dead, 3 cannot be traced and only 1 is known to be alive. Of the 16 operated on since 1930, 9 have recovered. Seven of these are less than 1 year old. The youngest patient was operated on when 40 hours old. Of the 7 deaths, 1 occurred five days after a phrenicectomy before herniorrhaphy was attempted, and 1 four days after operation, probably from pneumonia. The remaining 5 deaths were probably due to one or a combination of the following factors: failure to provide proper fluid balance, lack of positive pressure anesthesia or too tight closure of the abdominal wall. The last factor, the failure of sufficient room in the underdeveloped peritoneal cavity to receive the abdominal viscera, has been solved by closing only the abdominal skin, allowing the abdominal wall to stretch and suturing the peritoneum and the rectus muscles at a second operation in five or six days. There is sufficient evidence to confirm the futility of expectant or medical measures. The policy of waiting until the child gets older and stronger is apparently responsible for the loss of a great many lives that might have been saved by a timely operation. The authors state that on a theoretical basis an operation performed in the first forty-eight hours of life is advantageous. They have had 2 such cases. Their experience has shown that these infants stand major surgical procedures far better than at the end of a week or ten days. Within the first two days there is the advantage of dealing with the intestine before it becomes distended, with the possibility of replacing it in the abdominal cavity—which might otherwise be impossible. Preoperative treatment consists in making certain that the infant is in a proper state of hydration and that the intestine is deflated as much as possible. The latter can be accomplished by enemas, by gastric suction and by placing the infant in a tent with a high concentration of oxygen; from 90 to 95 per cent. Roentgen examination should always supplement the history and physical examination. A roentgenogram without the use of contrast mediums will usually give all the information that is necessary and is probably safer than giving barium to the baby.

Significance of Charcot-Leyden Crystals.—Thompson and Paddock examined the finger blood of 100 routine hospital admissions in which the diseases included hypertension, chronic nephritis, heart disease, pernicious and aplastic anemia, peptic ulcer, pneumonia, carcinoma, myelogenous and lymphatic leukemia, lymphosarcoma and Hodgkin's disease. The blood in none of these showed an absolute increase of the eosinophils and neither were Charcot-Leyden crystals demonstrated. Several patients were studied more thoroughly because of their disease or because of an unusual eosinophilia. Of 5 patients with bronchial asthma, none showed crystals in the blood. One patient with chronic ulcerative colitis had typical crystals in the stools but not in the blood. Of 3 patients with chronic myelogenous leukemia, 2 showed a number of crystals in the blood. The blood of 2 patients with presumed periarteritis nodosa showed Charcot-Leyden crystals in large numbers, as did that of a patient with presumed trichinosis with a leukocyte count of 16,000 and a 20 per cent eosinophilia. The blood of horses used for producing antiserum showed little eosinophilia and no crystals. The blood of normal rabbits showed no crystals even though their neutrophilic cells have an eosinophilic cast. Of 5 guinea pigs inoculated with Trichinella spiralis, none showed crystals. Prostatic secretion obtained after death produced no Charcot-Leyden crystals on standing for a week. After the addition of lead acetate to a filtered alcoholic solution of the secretion, quadrilateral crystals which resembled the crystals depicted in the literature as "spermin" were found. Microscopic examination of tissues from 11 fatal cases of myelogenous and lymphatic

leukemia revealed crystals in only 1 case; they were visible in all tissues of the body and were most plentiful in the pancreas and spleen. This patient had myelogenous leukemia. Of 7 patients with ulcerative colitis from whom sections of the colon were examined after death, 1 showed a marked increase of eosinophils in the submucosa, with occasional small Charcot-Leyden crystals. Slides of the lungs from 8 fatal cases of bronchial asthma showed crystals in 1; these were found in the mucus plugging the smaller bronchioles. Charcot-Leyden crystals appeared in blood in which a high absolute eosinophilia existed. They were not demonstrable by the same technic when eosinophils were not present in abnormally high numbers. The crystals are apparently not specific for any disease. The relation of the crystals to the eosinophils in all the diseases in which they were found seems to hold true. The nature of the crystals is not known. Attempts to isolate the crystals from the blood with a variety of solutions were unsuccessful; they were either dissolved or destroyed.

Southern Surgeon, Atlanta, Ga.

9:853-922 (Dec.) 1940

Lipoma of Colon. F. L. Barnes and J. P. Barnes, Houston, Texas.—p. 853.
Semen and Sterility. C. Rieser, Atlanta, Ga.—p. 862.
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Texas State Journal of Medicine, Fort Worth

36:527-590 (Dec.) 1940

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Hemorrhages in Late Pregnancy and Early Puerperium. J. E. Kanatser, Wichita Falls.—p. 552.
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Modern Mastoid Operation Performed with Electrically Driven Surgical Burs. S. Israel, Houston.—p. 563.
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Pellagra—Its Economic Importance. W. A. Hutchinson, Texarkana.—p. 568.

Yale Journal of Biology and Medicine, New Haven

13:161-292 (Dec.) 1940

*Infection with Virus of Choriomeningitis in Man. M. E. Howard, New Haven, Conn.—p. 161.
Local Ulcerating Action of Adrenalin. W. McFarland, New Haven, Conn.—p. 181.
Technic Suppressing Development of Reproductive Function and Sensitivity to Estrogen in Female Rat. J. G. Wilson, W. C. Young and J. B. Hamilton, New Haven, Conn.—p. 189.
Significance of Pain in Diseases of Female Pelvic Organs. A. H. Morse, New Haven, Conn.—p. 203.
Inhibition of Hair Growth in Dogs Receiving Estrogens. W. U. Gardner and J. DeVita, New Haven, Conn.—p. 213.
Diminishing Response of Skin to Frequently Repeated Reinfection with Invasive Bacteria. F. Duran-Reynals and E. Estrada, New Haven, Conn.—p. 217.
Therapy of Acute Staphylococcic Infection of Mice with Antitoxin and Sulfonamide Compounds. M. Tager, New Haven, Conn.—p. 237.
Preventive Medicine at the Yale University School of Medicine. J. R. Paul, New Haven, Conn.—p. 253.
*Effects of Gastrointestinal Resections in Swine on Antianemia Potency of Liver: Observations on Nature and Sources of Materials Effective in Pernicious Anemia. A. J. Geiger, L. S. Goodman and L. N. Claiborn, New Haven, Conn.—p. 259.
Relation of Estrogen to Ossification and Levels of Serum Calcium and Lipoid in the English Sparrow, Passer Domesticus. C. A. Pfeiffer, A. Firschbaum and W. U. Gardner, New Haven, Conn.—p. 279.

Infection with Virus of Choriomeningitis in Man.—Howard discusses diverse manifestations of 8 cases found among 33 with a variety of neurologic signs and a lymphocytic response in the spinal fluid. In 6 of the 8 the choriomeningitis virus was isolated from the spinal fluid and after death it was found in the cerebral tissue of the remaining 2. The cases were divisible into infection without meningeal or neurologic signs, and benign lymphocytic meningitis and encephalitis, which may be mild, prolonged or fatal. The first case presented no neurologic signs and the complaint of persistent headache prompted the lumbar puncture, and the second case was a typical benign lymphocytic meningitis. The virus was isolated from these patients nine and five days, respectively, after acute onset. Encephalitis of varying severity was found in the next 4 cases. The third and fourth cases were relatively mild; recovery was fairly prompt and without sequelae. The onset was insidious in the fifth case and the course prolonged. Death was sudden in the sixth case. It occurred five months after onset, when improvement in the mental status was beginning to be noticeable. In the milder cases the virus was isolated from the spinal fluid early in the course of the disease; in the more severe and prolonged forms it was found as late as fifty-nine days after onset. Among these 6 cases the lymphocytic response in the spinal fluid was highest in the meningeal form of the disease. The cell count was within normal limits in the fifth and sixth cases; a positive Pandy or an increased protein content was demonstrable. Therefore it seems that the cell count is of no prognostic significance as to the seriousness of the disease. In neither instance of hemorrhagic encephalitis was the virus isolated from the spinal fluid. The pathologic picture in these two cases was that of widespread hemorrhagic lesions involving the subcortical white matter of the brain and cord in one and both the gray and white matter in the other. The meningeal reaction was slight and in both instances the choroid plexus was free. No inclusion bodies were found. The inoculation of fresh brain tissue into mice and guinea pigs from the seventh case failed to produce symptoms. The incubation period in the guinea pig and the chicken following inoculation with material held in glycerin for seventy days was long. This gives rise to doubt as to the validity of the observations. The later discovery that lesions were in the subcortical white matter prompted the author to try again with the small amount of remaining material. Work is now in progress to determine whether a latent or slowly developing infection in guinea pigs may be produced when the inoculating dose is small. From the data at hand this seems to be the case. A 10 per cent emulsion of brain tissue from the eighth case from the right temporal and right parietal lobes after storage in glycerin for seventy days produced fever in nine days in 1 instance and in fourteen days in 3 instances after combined intracerebral and subcutaneous inoculation into 4 guinea pigs. Death occurred eleven, twenty-three, thirty and thirty-seven days respectively after inoculation. Mice showed no evidence of infection and later succumbed to reinoculation with the Rivers W. E. strain. Failure to demonstrate neutralizing antibodies in the blood of the first and fourth patient is a source of concern, as the final proof is thereby lacking that the infection was really due to the virus of choriomeningitis. The spinal fluid of the other 25 patients, for whom a variety of diagnoses were later proved, was similarly studied and no virus was obtained. These served as controls and added to the evidence that choriomeningitis virus was not present among the stock animals in use.

Gastrointestinal Resections and Antianemia Potency of Liver.—Geiger and his co-workers tested the theory of liver storage of the antianemic principle by removing the stomachs from 7 swine and then determining whether their livers showed progressive depletion of the effective factor. The results of the experiments are summarized as follows: 1. Extirpation of the stomach in swine results in progressive depletion of the antipernicious anemia principle of the liver and complete exhaustion of liver potency within six months. This suggests that the liver stores or elaborates and stores a product furnished by the stomach. 2. Similar exhaustion is observed when the stomach is retained but isolated within the animal. This suggests that the effective factor results from gastric digestion rather than from an internal secretion of the stomach. 3. The livers of newborn pigs from a normal sow contain the anti-pernicious anemia principle, while those of newborn pigs from an agastric sow do not. This confirms the view that the effective factor is a product of gastric digestion. 4. Extirpation of the duodenum in swine diminishes the liver's content of the principle, which indicates that the duodenum is a true source of Castle's intrinsic factor.

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

British Medical Journal, London

2:657-692 (Nov. 16) 1940

Today and Tomorrow. J. A. Ryle.—p. 657.
*Pathogenesis of Nonpulmonary Tuberculosis. M. C. Wilkinson.—p. 660.
Stab Wounds of Chest. T. Schrire.—p. 662.
Atropine Poisoning: Description of Unusual Case. A. B. Carter.—p. 664.
*Perforated Peptic Ulcer: Review of 175 Personal Cases. J. C. Ross.—p. 665.
Amnioplastin: A Warning. W. Penfield.—p. 668.

Pathogenesis of Nonpulmonary Tuberculosis.—Wilkinson discusses the relation between tuberculosis of the lymph nodes and hematogenic tuberculosis. He bases his remarks on the data obtained from 593 persons with nonpulmonary forms of the disease who between 1930 and 1937 were admitted to the Essex County Council Sanatorium, Black Notley. Skeletal tuberculosis was the most common form of nonpulmonary tuberculosis at all ages, renal tuberculosis developed most often in young men, tuberculous peritonitis was more common in female than in male patients and was most frequent in adolescence, and the majority of patients with lymphatic tuberculosis were children. Patients admitted with tuberculosis of the thoracic nodes are not included in the series. Nonpulmonary hematogenic tuberculosis or tuberculous bacillemia was found to be evenly distributed, that is bilateral. Twenty-two of the 28 patients with renal tuberculosis had a complete examination and showed evidence of bilateral infection. Similarly tuberculous epididymitis was found to be bilateral in most patients, although it was not always manifest simultaneously in both epididymides. Nine of 13 patients suffering from tuberculous salpingitis were known to have bilateral disease. The author states that tuberculous peritonitis may occur as a direct extension from tuberculous abdominal nodes, but in his opinion it occurs more commonly as a hematogenic tuberculous infection or as an ascending peritonitis from tuberculous fallopian tubes. When the infection is hematogenic, miliary tubercle along the blood vessels may be seen at operation. Tuberculous pleurisy is a commonly associated lesion. It occurred in 6 of his patients. Of the patients with tuberculosis of the lymph nodes, 119 were admitted for tuberculous cervical adenitis and 40 for tuberculous abdominal nodes. No associated tuberculous lesions were found. Follow-up reports of 81 were received from a few months to seven years after discharge, and in no case had a fresh tuberculous lesion developed in another part of the body. The results of examination for evidence of past or present glandular tuberculosis in 134 patients suffering from skeletal, peritoneal or genito-urinary tuberculosis (diagnosed by roentgen evidence of calcification in the chest or abdomen) show no evidence of tuberculosis of the cervical glands; neither was there any gross evidence of past or present glandular tuberculosis. However, this does not mean that the patients did not suffer from some degree of lymphatic tuberculosis at the time of their primary infection, as in some patients the glandular tuberculosis may have subsided before the roentgenogram was taken or enough time may not have elapsed for calcifications to develop. The study shows that conversely patients with hematogenic tuberculous lesions do not necessarily show evidence of previous gross glandular tuberculosis. Therefore it may be inferred that gross glandular tuberculosis is not necessarily associated with severe tuberculous bacillemia and may, on the contrary, be a means by which severe hematogenic infection is prevented. It appears that the severity of hematogenic tuberculous infection is not proportional to the severity of glandular tuberculosis and that hematogenic tuberculous lesions are not likely to appear if the glandular tuberculous lesion following primary infection is treated by constitutional measures. Under favorable conditions the lymphatic system may afford some protection against the entrance of tubercle bacilli into the blood stream. Not only may the cervical, thoracic and abdominal nodes be a barrier to the blood stream entrance of tubercle bacilli from the site of primary infection, but the regional glands may exert the same function. The disastrous effects of tuberculous infection in infants are to some extent modified if the lymphoid tissue is well developed and if the child's environment and nutrition are good.

Perforated Peptic Ulcer.—Ross presents the follow-up data of 89 out of a personal series of 175 cases of perforated ulcer observed by him during 1930 to 1940. Fifty-one of the 89 patients have no symptoms and are following their previous vocation, 28 have trivial or occasional mild symptoms causing no inconvenience or loss of time from work and 10 have symptoms that are severe enough to cause absence from work. The follow-up suggests that, provided the patient adheres to a strict dietary for six months after operation and maintains dietetic care thereafter, his prospects are good. However, many symptom-free patients stated that they were taking no dietetic precautions. The patient's occupation often gives rise to difficulties, as lorry drivers, bus drivers, tram conductors and the like have not the same dietetic facilities as persons in other trades. In assessing the immediate outlook the number of hours between the perforation and operation is the most important single factor. Among the 175 cases there were 28 (16 per cent) deaths; in 19 of these the delay ranged from three hours to seven days; the average was twenty-five and a half hours. If 2 cases delayed for five and seven days respectively are excluded, the average period between perforation and operation among fatal cases was ten and four-tenths hours. The remaining 9 cases were simply described as "late." The site of the ulcer is another important factor; the perforated gastric ulcer is regarded as having a somewhat worse prognosis. The prognosis for duodenal, pyloric and juxtapyloric ulcers appears to be identical. While it has been generally recognized that perforation and hematemesis are usually fatal, it has been overlooked that any intercurrent disease renders the prognosis infinitely worse, irrespective of the two foregoing factors. In the author's series, among the deaths, it was established that before operation 6 patients had had angina, chronic myocarditis or auricular fibrillation, 2 chronic bronchitis, 3 diabetes mellitus, 1 chronic nephritis, 1 exophthalmic goiter and 1 syphilis. Thus in 50 per cent of the fatalities an intercurrent disease was present. The most dangerous period appears to be three or four days after the operation, death being probably due to peritonitis and toxemia. The operation should consist of simple closure of the perforation and removal of the peritoneal fluid, together with drainage through a suprapubic stab incision when the fluid is thick, and in late cases. Gastroenterostomy at the original operation is contraindicated because the operation is unjustifiably lengthened; the perforated ulcer may be of the "acute" type and, should a subsequent operation become necessary, a gastroenterostomy is rarely the wisest and most efficacious procedure.

Medical Journal of Australia, Sydney

2:423-452 (Nov. 2) 1940

Acute Rheumatism. L. Hughes.—p. 423.
Radical Operation for Cancer of Breast Under Local Anesthesia, with Account of Technic: Fifty-Five Cases. C. E. Corlette.—p. 427.
Pink Disease: Consideration of Three Etiologic Possibilities. F. W. Clements.—p. 430.
Inquests and Experiences in the Coroner's Court. J. B. Cleland.—p. 433.
Gas Tensions in Tissues of Normal Resting Subjects. E. W. Sibree.—p. 436.

2:453-486 (Nov. 9) 1940

Problems Relating to Supply of Medical Equipment. A. Newton.—p. 453.
Injuries of Flexor Tendons of Hand. L. O. Betts.—p. 457.
Delayed Union in Fractures. F. H. M. Callow.—p. 460.
Shoes as a Deforming Influence on Feet. A. R. Hamilton.—p. 462.
Treatment of Late Contractures Resulting from Erb's Palsy. A. Meehan.—p. 464.
Hoke Operation for Stabilization of Feet in Poliomyelitis. Elizabeth McComas.—p. 465.
Para-Articular Calcification of Shoulder: Survey. L. Macdonald.—p. 467.

2:487-520 (Nov. 16) 1940

Some Aspects of Pertussis Immunization. Dorothy Gepp.—p. 487.
Irrational Medical Practice. H. Priestley.—p. 489.
Simplified Blood Transfusion Technic with Controlled Positive Pressure and Automatic Blood Agitator. E. H. Hipsley.—p. 492.
New Diagnostic Method: Manipulation of Hypersensitive Visceral Reflex as Clue to More Exact Diagnosis. F. Trinca.—p. 493.
Function in Relation to Alinement in Treatment of Fractures. S. Scougall.—p. 496.
Notes on Pregnancy and Parturition in D'Entrecasteaux Islands. E. Ford.—p. 498.
Hematuria: Diagnosis and Treatment. R. G. S. Harris.—p. 501.

Presse Médicale, Paris

48:737-760 (Sept. 18-21) 1940

*Treatment of Penetrating Wounds of Thorax. R. Monod.—p. 737.
Haemophilus Influenzae Meningitis. C. Gernez and C. Huriez.—p. 740.
*Present Day Foundations for the Treatment of Bronchiectasis. P. Santy and M. Latarjet.—p. 743.
Galvanotherapy in Poliomyelitis. H. Bordier.—p. 746.

Penetrating Wounds of Thorax.—Monod discusses treatment of pleuropulmonary uncomplicated wounds of average gravity. These constitute 30 per cent of all chest wounds incurred in war. He classifies three types and indicates the nature of the intervention: (1) lesions accompanied by serious hemorrhage, (2) lesions presenting the risk of infection due to presence of shell or bomb fragments and (3) uncomplicated cases. If in spite of sedative medication and immobilization a progressive aggravation is observed, intervention is indicated. Open chest wounds can be enlarged to determine the source of the hemorrhage. In closed chest wounds or those presenting small perforations, whether thoracic or extrathoracic, a wide exploratory thoracotomy is in order. Hundreds of cases of the second type proved at necropsy that enclosed shell or bomb fragments presented a serious risk of infection. In the determination of the operative procedure, great importance is attached to the embedded foreign body itself, to roentgen ray evidence and to presence of costal and scapular fractures. Wide thoracotomy is to be performed, especially if fragments are lodged juxtapleurally and fractures are involved. In uncomplicated cases thoracotomy is delayed and watchful observation is practiced. Excision of the parietal wall wound is always to be made no matter how insignificant the cutaneous lesion may be for a great deal of muscular damage may be concealed. Respiratory disorders need to be noted, frequent bacteriologic tests made and drainage promptly applied. Pleural infection may occur in the absence of a hemothorax. High initial pyrexia has a tendency to fall spontaneously. Men with thoracic lesions should be assigned to a special service division where they may receive further care for empyema and where secondary removal of foreign bodies may be performed. Evacuation should not be attempted until the end of the second week. The author cautions that a badly supervised empyema will lead to pleural fistula and a chronic condition which necessitates serious surgical intervention. He stresses the fact that thoracic wounds require medical care until the wound has completely healed.

Treatment of Bronchiectasis.—According to Santy and Latarjet, a study of the recent, especially the English and American, literature discloses the progressively favorable results, immediate and late, obtained by lobectomy and pneumonectomy in bronchiectasis. The prognosis, the value of conservative preoperative treatment, the indications and the contraindications for surgical intervention are increasingly better understood. Spontaneous recovery, under conservative management, can be expected only in "dry" cylindric cases of bronchiectasis resulting from a previous infection. Some "dry" hemoptysic cases in which roentgenograms taken with a radiopaque substance (iodized oil) and the endoscope reveal lesions need promptly to be surgically treated. In spite of their apparent benignity, these cases invite new hemorrhages and secondary infection of the cavities. The essential service of conservative therapy, working with appropriate clinical and laboratory controls, lies in conditioning the infected patient for the operative act. The mortality incidence for partial pulmonary extirpations extending over ten years amounted to 10 per cent of the cases treated. Subsequent series have been without a single fatality in the experience of some authors. The mortality rate for total extirpation was from 18 to 20 per cent. Children were observed to tolerate both operations better than adults. In 166 cases of lobectomy, cited from Tudor Edwards, involving 38 children aged from 4 to 16 years, there were no deaths (0.0 per cent). In 16 adults aged from 40 to 50, there were five deaths (31 per cent). In a summary of 239 cases (lobectomy and pneumonectomy) collected from different authors, 172 were completely restored functionally and anatomically (70 per cent) and good results were obtained in patients restored to normal living but requiring subsequent medical attention. In the latter group the roentgenogram was either unable to detect residuary lesions or iodized oil penetration was insufficient, especially in the lingular process of the left upper lobe. The authors discuss the value of postural drainage, the indications for one stage and two stage interventions (preoperative artificial creation of adhesions), the value of early diagnosis and the need of complete radiopaque delineation of the whole bronchial tree in both lungs. Localized bronchiectasis will yield only to surgery. Mortality resulting from pulmonary exeresis is chiefly due to infectious complications.

Anais Brasileiros de Ginecologia, Rio de Janeiro

10:391-470 (Nov.) 1940. **Partial Index**

*Germ Cell Damage from Roentgen Irradiation. C. Salgado and J. Ferolla.—p. 391.
Hormone Therapy in Gynecology: Some Aspects. F. V. Rodrigues.—p. 418.

Germ Cell Damage from Roentgen Irradiations.—Salgado and Ferolla review the literature on the clinical application of gynecologic roentgen irradiation and the possibility that the latter may cause harm to germ cells. They refer particularly to the work of Muller, which proved the existence of roentgenologic changes in "Drosophila melanogaster." The changes attributed to roentgen irradiation correspond to a condition defined as early germ cell damage. A late genetic damage has not been proved so far. Its demonstration would interdict gynecologic irradiation, but this does not seem to be the case. The authors irradiated the lumbar region of rats with doses of from 2.4 to 5.6 roentgens. Sixteen days later the animals were given to the males. The first generation consisted of 52 animals, all normal in appearance, conformation of the eyes, development of the body and behavior. The rate of mortality in the animals was the same as in the offspring of nonirradiated animals. By the end of the experiment a total number of 118 adult rats from the irradiated original ancestors were obtained in five consecutive generations. Through the generations all the animals were normal in all respects and procreated by endogamy.

Revista Mensual de Medicina, Mexico City

2:89-116 (Oct. 15) 1940. **Partial Index**

Treatment of So-Called Prostatic Adenoma. A. Madrid.—p. 89.
*Poisoning with Barbituric Acid Compounds. R. Leñero.—p. 97.

Strychnine in Poisoning with Barbituric Acid Compounds.—Leñero reports encouraging results from large doses of strychnine in more than 100 cases of acute poisoning with barbiturates. The treatment should be commenced as early as possible in doses of 200 mg. for the first two hours, up to a total of 1,300 mg. for the first twenty-four hours. The drug is administered intravenously in isotonic dextrose solution. The acuteness of the condition when the victim is first seen, age, abnormalities of the viscera, pregnancy and the presence of associated poisoning do not contraindicate its use. The degree of saturation with the drug in the course of treatment is appreciated by the Chvostek sign. The author concludes that strychnine in large doses should be resorted to immediately in cases of barbituric coma, as well as in accidents during administration of evipal soluble and similar barbituric anesthetics.

Deutsche medizinische Wochenschrift, Leipzig

66:981-1008 (Sept. 6) 1940. **Partial Index**

Prognosis in Disturbances of Internal Secretion. H. Marx.—p. 983.
Prognosis of Pernicious Anemia. H. Schulten.—p. 986.
*So-Called Irritable Soldier's Heart. D. Thomas.—p. 989.
Clinical Significance of Sternal Puncture. S. Thaddea.—p. 992.

Irritable Soldier's Heart.—Thomas points out that a healthy person experiences dyspnea during physical exertion which persists for varying periods. After long and severe exertions, signs of exhaustion appear in the form of tremor, weakness and later of fatigue and pain. Pulse rate and blood pressure are increased, respiration is accelerated, the apex beat is often prolonged and forceful, and systolic murmurs are frequent. These are signs of the physiologic effort syndrome. This syndrome develops more readily in weak persons than in the average person. It is frequent in young soldiers but is not a specific soldier's disease. The so-called irritable soldier's heart is one of the ordinary chronic defects of city dwellers who lead sedentary lives. It is erroneous to designate this defect as

heart disease. The majority of such persons are emaciated and have weak muscles and a long and narrow chest. Some are nervous as indicated by the ease with which their emotional reactions are elicited. The author examined functional capacity of the heart of men with so-called soldier's heart by means of Rein's basal metabolism recorder. He found that men with soldier's heart differ from normal men by a lesser utilization of the ventilation oxygen, great alterations in the respiratory volume, prolongation of recovery time for respiration and slight utilization of oxygen. It is difficult to estimate the functional capacity of the so-called soldier's heart. Many of these men are weak and incapable of great physical exertion. The history often reveals that during the years of growth they had been excused from physical exercises partly because they failed in great exertions and partly because a systolic murmur had been regarded by the physician as indicative of heart disease. This classification as a sufferer from heart disease had an unfavorable psychologic effect. It is a mistake to keep these men away from all physical exertion. Cautious and gradually increasing physical exertion often accomplishes good results. These persons should not exert themselves to a point at which they feel exhausted, but long enough for the respiration to become noticeably accelerated and deepened. The author found that men in whom signs of soldier's heart are mild or moderate can be developed into capable soldiers.

66:1037-1064 (Sept. 20) 1940. Partial Index

*Prognosis of Obesity. E. Grafe.—p. 1037.
Therapeutic Results with Sulfanilamide Pyridine in Epidemic Meningitis. G. Säker.—p. 1039.
Goiter and Treatment of Hyperthyroidism, Inclusive of Toxic Goiter. W. May.—p. 1042.
Qualification for Service in the Tropics. P. Mühlens.—p. 1045.
General Surgery in the Tropics. E. Gminder.—p. 1046.
Therapeutic Efficiency of Dioxydiethyl Stilbene. E. Keeser.—p. 1049.

Prognosis of Obesity.—Grafe cites statistics which indicate that life expectancy of obese persons is less than that of persons of normal weight. This should be impressed on obese persons in order to give them the will necessary for the effective treatment. If the age of 40 is taken as the starting point, the chances to reach the age of 80 are only one third as favorable in the obese as in those of normal weight. Obese octogenarians are a great rarity. It is necessary to differentiate between what is theoretically attainable and what can be accomplished in view of human shortcomings. Theoretically obesity is curable, even in the severe cases, as far as no irreversible changes have yet developed. Obesity develops as the result of a positive energy and water balance and it can be counteracted only if these balances are negative for a long time. The dietetic treatment is most important; the nutrition must be subnormal in calories. In the beginning it should provide 30 per cent of the requirements and less and should gradually be increased to from 50 to 75 per cent. Many begin with a fasting cure. The author usually begins the reducing treatment with a fast of several days' duration, but he thinks that it is never necessary to continue this fast for two or three weeks. Whether to extend the days of fasting depends chiefly on how the patient reacts to hunger and what his mental attitude is. There are no strict contraindications, but no patient should ever be forced to fast. In prescribing a diet it is essential that the patient be given exact quantitative regulations with careful computation of calories, and the patient must carefully weigh all the food. The fluid and sodium chloride intake must also be carefully controlled, because the adipose patient is not only lipophil but also hydrophil. The total fluid intake should not exceed 0.75 liter and the salt content must be reduced to the point at which the food remains just eatable. Medicinal therapy is necessary in some cases. Salyrgan is helpful in counteracting the hydrophilia of the obese person. The diuretic effort can be intensified by acidification of the organism with ammonium chloride. In severe cases of obesity, particularly in those in which endogenic or constitutional factors are involved, thyroid preparation can be given. Contraindications to this treatment are severe organic cardiac defects, glycosuria and diabetes. There are hopelessly careless obese persons who lack the will power for effective treatment, but there is no incurable obesity. There are patients who, in spite of rigorous dieting, do not lose much. These patients lose fat, but they retain water, so that the weight remains unchanged for days or weeks. However, later this water is eliminated either spontaneously or with the aid of diuretics.

Fortschritte a. d. Gebiete der Röntgenstrahlen, Leipzig

62:67-144 (Aug.) 1940

Variations and Defective Formations in Structure of Osseous Thorax. L. Stehr.—p. 67.
Depression of Esophagus Caused by Arteria Subclavia Dextra That Originated on Left Side. M. Dahm.—p. 108.
*Has Roentgenologic Diagnosis Improved the Therapeutic Results in Gastric Cancer? H. Bade.—p. 114.
Increase in Conduction Capacity of Water by Action of Roentgen Rays. *R. Reiter.—p. 122.

Roentgenologic Diagnosis of Gastric Cancer.—Bade studied 107 patients with gastric cancer in order to determine whether the improvement in roentgenoscopy produced better therapeutic results. He chose patients under 40 because of a greater possibility of error among younger patients. He found that there was no increase in the number of operable cases despite the fact that 75 per cent of patients with gastric carcinoma have a long history of gastric disorders. An early roentgenologic examination by one experienced in this technic is of great importance. Control examinations to check negative results are necessary but are rarely carried out. There is danger of erroneously diagnosing cancer as ulcer, for their roentgenologic differentiation is often impossible. The differentiation may be impossible even at operation. It is advisable for this reason to resort to resection if the niche fails to decrease on a dietetic regimen. Tumors which appear benign in the roentgenogram should be operated on, because of the possibility of differentiating with certainty benign from malignant tumors. A roentgenologically detected ulcer subjected to dietetic treatment requires control examinations. Should the niche fail to decrease, gastric ulcer in contradistinction to duodenal ulcer should be resected early. A carcinoma may exist even if the niche decreases and the patient is free from complaints. The author observed one such case. The author is convinced that the extremely unfavorable therapeutic results can be improved if polyps and other benign tumors are accepted as an indication for an operation.

Kinderärztliche Praxis, Leipzig

11:277-316 (Sept.) 1940. Partial Index

Increase of Nubecula as Precursor of Perforation of an Abscess into the Bladder. K. Stolte.—p. 277.
*Fever Therapy of Poliomyelitis. H. Kohl.—p. 278.
*Congenital Tuberculosis. E. Keyser.—p. 284.

Fever Therapy of Poliomyelitis.—Kohl subjected in 1936 2 children with poliomyelitis to two series of fever treatments, the fever being induced by a bacterial protein preparation. The results of this form of fever therapy proved unsatisfactory. He treated 8 children with poliomyelitis with malaria. The fever treatments with the bacterial protein had been given two and three months after the onset of the poliomyelitis, and the malaria therapy from three to six weeks after the onset. In spite of the earlier treatment, however, the results were not encouraging. The author gained the impression that the same improvement in motion might have been obtained with the measures customarily employed at the Leipzig clinic. He reports histories of children subjected to malaria treatment and shows that at most in 3 cases a slight improvement might have been due to the fever therapy.

Congenital Tuberculosis.—Among 79 tuberculous nurslings Keyser observed 1 in whom the disease was definitely congenital. This child was born to a mother who had a productive, infiltrative pulmonary and laryngeal tuberculosis and who died from tuberculosis one month after the birth of the child. The infant had been removed from the mother immediately after birth and was cared for in an environment free from tuberculosis. The child developed normally the first three weeks after birth, at which time fever and nutritional disturbances appeared. Roentgen examination revealed a bilateral, coarsely nodular pulmonary tuberculosis, and the gastric juice contained tubercle bacilli. The child died on the thirty-fourth day of life, and the necropsy disclosed a bilateral, caseous, nodular pulmonary tuberculosis with involvement of the hilar

lymph nodes. The history and anatomic features of the case indicate a congenital or at least connatal character of the infection. The anatomic picture was typical for cases of this type when compared with the 5 cases reported in the literature. All these infants had a disseminated, nodular pulmonary tuberculosis. In all of the cases the primary focus could not be demonstrated. The author assumes that this disseminated nodular pulmonary tuberculosis of the first two months of life, in which it is impossible to find a primary focus, represents a primary colonization of tubercle bacilli which can take place only by way of the blood stream or by the aspiration of amniotic fluid containing tubercle bacilli.

Medizinische Klinik, Berlin

36:855-882 (Aug. 2) 1940. **Partial Index**

Bacterial Food Infections. K. Beckmann.—p. 855.
Injuries Produced by Chemical Warfare and Their Treatment. O. Hoche.—p. 857.
Preparation for Ambulatory Insulin Therapy. H. Malten.—p. 860.
Combat of Rickets. E. Türk.—p. 862.
*Rheumatic Articular Disease and Trauma. G. Jorns.—p. 865.

Rheumatic Articular Disease and Trauma.—Jorns points out that rheumatic changes in one or several joints are sometimes ascribed to accidental injuries. The assertion is often based on mere conjecture. The author presents a survey which indicates the deviousness of the attempts to deduce from the presence of a locus minoris resistentiae supposedly produced by a trauma, and the possibility that pathogenic organisms circulate in the blood. He thinks that it is more feasible to accept individually differing association rather than generally applicable relations. The factors leading to the development of pyogenic metastases should be looked for not only in the type of the pathogenic organism but also in the patient's body and here less in the local tissue injury than in the general status of susceptibility. In view of the predisposition of rheumatic infections for the joints, the action of a preceding trauma can be regarded as dispensable. Moreover, it would have to be explained in what manner the traumatic injury produces the prerequisites for the development of rheumatic articular changes. This question is pertinent in view of the fact that the morphologic aspects of rheumatic polyarthritis are such that the association of trauma can be dispensed with. Before more is known about the cause of rheumatic infection, caution is necessary in the evaluation of a possible connection between trauma and articular rheumatism. A causal connection can be accepted only if the following prerequisites are fulfilled: 1. The rheumatic process must develop in the injured joint. 2. Considerable force must have been exerted. 3. The rheumatic lesion must correspond with the trauma in location as well as in time. The author points out that if trauma and infectious rheumatic process concur there is the danger that the direct results of the trauma are regarded as rheumatic and are treated incorrectly.

Medizinische Welt, Berlin

14:397-420 (April 20) 1940

Tuberculosis of the Larynx. H. Alexander.—p. 397.
Diagnostic Errors and Curiosities in Tuberculosis Clinic. F. Lommel.—p. 401.
*Conservative Obliteration of Varicose Veins or Surgical Procedure? J. Neideck.—p. 403.

Conservative Treatment of Varices.—Neideck recommends sodium chloride injections in the treatment of varicose veins. The technic consists in injecting not more than 20 cc. in toto of a sodium chloride solution (1:3 concentration) into varices at intervals of three days. Puncturing is done distally, slowly proceeding in an upward direction, with the patient in a sitting position. Troublesome phlebitis can be prevented by the utmost cleanliness in the instruments and in disinfection of the skin. Venous impermeability, damaged renal parenchyma, staphylomycosis and the presence of febrile disease or of a thrombophlebitis are contraindications. In pregnancy, a gynecologic examination should be made first. Reactions to injections vary from case to case, since the destruction of the varicose channels is not always the same. The danger of paravenous infiltration may be met by promptly injecting from 10 to 20 cc. of the patient's cubital venous blood into the endangered tissue area or by a saline solution. The author believes that the conservative treatment of varices does not yet enjoy the consideration which it deserves.

14:1061-1084 (Oct. 19) 1940

*Theory and Practice in Chemotherapy of Gonorrhea. H. T. Schreus.—p. 1061.
*Roentgen Therapy in Dementia Paralytica and Tabes. F. Bering.—p. 1066.
Things to Be Observed by the Practical Physician in Examination of Gastrointestinal Diseases. R. Kühn.—p. 1068.

Chemotherapy in Gonorrhea.—Schreus discusses the use of various sulfonamide preparations in gonorrhea, the dosage, prevention of relapses and sequels. Nothing is gained by including hours of the night into a therapeutic program which provides for three to four single daily doses. Concentrated doses given orally for three to five days are sufficient to produce a cure, if a cure is possible. Cases which respond slowly to drug action, though negative after long-continued medication, are often liable to relapses in the end. Massive doses given over a shorter period of time are better tolerated than those of lower concentration administered for a longer time. Drug treatment, routinely continued for prophylactic purposes after the patient has been demonstrated to be gonococcus negative, is unnecessary and harmful. Optimal dosage is regarded as consisting in the compatibility of high concentration levels with the ability of the patient to tolerate them. Actual cure is determined by the absence of the micro-organism in cultural assays. In addition, two provocative tests are applied, one immediately after the conclusion of the treatment, the other a week later, and the patient is kept under clinical and laboratory observation for two weeks longer. To induce abundant urinary excretion, compound solution of iodine in a 1:6 concentration was found effective. A refractory tendency to sulfonamide therapy in primary gonorrheal infection is now met by vaccination or by nonspecific stimulation ten days before the drug treatments are begun. Sequels were few and negligible. Hepatic damage, originally observed in a few cases, in subsequent investigations was no longer determinable by relevant laboratory examinations. Cyanosis was not equally induced by the various preparations and is possibly due to the aniline element in the sulfonamides. It readily yields to methylthionine chloride. Chemotherapeutically stubborn cases were often seen to react remarkably well to local treatment when local treatment was applied concomitantly or soon after the termination of the other treatment.

Roentgen Therapy in Dementia Paralytica and Tabes.—Bering summarizes two years of observations of the value of roentgen therapy in dementia paralytica and tabes, based on 130 cases. Cranial application of irradiation to patients with dementia paralytica was suggested by the favorable results obtained roentgenologically on abscesses of the axillary apocrine glands. The case material consisted of persons in whom malarial therapy was either contraindicated or had to be discontinued because of cardiac disorders or had left sequels such as headache, malaise and lassitude. The efficacy of roentgens is conditioned on the extent to which anatomic changes, both inflammatory and degenerative, have taken place in the brain. These cannot always be determined. The meninges are more or less strongly indurated. The radiosensitive endothelial cells show proliferation and edema in the vessels of the cerebral cortex and in the larger vessels. All portions of the brain are pathologically affected; the frontal most, the occipital least. The particular considerations entering into the management of each case are governed by the clinical and cerebrospinal fluid observations. No definite conclusions can yet be formulated regarding the usefulness of roentgen therapy in dementia paralytica. In a number of cases subjective and objective amelioration was achieved which still persisted after eight months. In general, irradiation was found to have an effect on the clinical manifestations of dementia paralytica, especially in incipient stages, and on the cerebrospinal fluid comparable, at least, with that of malarial therapy and hence applicable in cases in which the latter treatment is not permitted. Moreover, its action was more prompt. Lymphocytes in the spinal fluid were observed to decrease rapidly. The patients often gained weight. Often headaches and malaise were cleared up and the memory was seen to improve, the roentgens thus favorably influencing inflammatory sites that had not responded well to malarial therapy. Roentgen action on the frontal lobes not infrequently clarified the mind, increased the appetite and stimulated the desire to

work, as the result, no doubt, of the favorable effect on the augmented endothelial cells of the endarteritic processes. Roentgen therapy is not intended to replace malarial therapy. Best results are obtained in early diagnosis. There are no contraindications to the treatments. Outpatient service does not interfere with the economic life of the patient. A temporary complete loss of hair must be reckoned with. Roentgen therapy for tabes was not encouraging, though some favorable results were achieved.

Münchener medizinische Wochenschrift, Munich

87:985-1016 (Sept. 13) 1940. **Partial Index**

Mental Disturbances After Gunshot Wounds of Brain. A. Bostroem. p. 985.
*Early Diagnosis of Carcinoma of Colon and Timely Surgical Treatment. U. Graff.—p. 988.
Case of Pernicious Anemia Refractory to Liver Therapy. A. Bingel.—p. 993.
New Points of View on Problem of Prolonged Pregnancy. E. Tscherne and E. Engelhart.—p. 996.
Clinical Aspects of Perthes' Disease. E. Schrader.—p. 999.
Favorable Modification of Diabetes Mellitus in Acromegaly by Irradiation of Hypophysis with Some Observations on Hypophysectomized Dogs. J. Bauer.—p. 1002.

Early Diagnosis and Treatment of Carcinoma of Colon.—According to Graff the unusually frequent concurrence of polyps and carcinoma of the colon is significant and necessitates careful examination and continued observation. Polyposis is often hereditary and the carcinomatous degeneration is likewise frequently a familial trait. Colon carcinoma is amenable to a complete surgical cure, because it grows slowly and metastasizes late; but, in spite of this, a high percentage of carcinomas prove inoperable at the time of operation. The results of surgical treatment could be greatly improved by earlier diagnosis. There are three stages in the carcinoma: (1) the stage of clinical latency, (2) the stage of gastrointestinal manifestations and (3) the stenotic stage. During the first stage the diagnosis is always more or less accidental. The correct interpretation of the symptoms of the second stage decides the fate of the patient. Only a few of the symptoms are associated with the focus of the disease. General discomfort, fatigue, feeling of fulness and of pressure after eating and flatulence are the chief symptoms. Pallor, gastric disturbances and occasional colics complete the picture of the early second stage, but gradually stenosis develops and this considerably facilitates the diagnosis. If operation were done during this stage, it would still have a favorable prognosis. Conservative treatment is justified only when carcinoma can be definitely excluded. Especially the comparatively mild disorders of incipient stenosis with spasmodic pains in the abdomen, irregularities of the formerly regular defecation, meteorism, pallor, mild anemia and loss of weight must be taken as strongly indicative of colonic cancer. They make it imperative to use all diagnostic aids. Clinical examination by means of inspection and palpation should be complemented by laboratory tests. The examination of feces for mucus and blood may be valuable, but only identical results in repeated examinations are reliable. Mild hypochromic anemia and occasional leukocytosis are suggestive but by themselves are of no particular value. The same applies to the sedimentation speed of the erythrocytes. Although it is often greatly increased in malignant tumors, it is not necessarily so. The outcome of cancer reactions likewise cannot by themselves be taken as an indication for operation. The most important diagnostic measure is the roentgen examination with the best available apparatus and technics and with various exposures. Even this method has its limitations. Incipient carcinomas without ulcerations, and small carcinomas hidden behind a fold of mucous membrane may escape detection. Moreover, the differentiation of benign and malignant stenoses and the exclusion of spasm is often difficult. Exploratory laparotomy should be resorted to, after all other examinations have failed and yet colon carcinoma is suspected. Alternate diarrhea and constipation, loss of weight, admixture of blood and mucus to the feces and persistent contraction of the intestine above the stenosis are usually regarded as the cardinal symptoms, but the author points out that they are not present in more than 60 per cent of the cases. Ileus is the most frequent and the most feared complication. Abscess is another dangerous complication. Intense peristalsis may cause early invagination of a small tumor. Severe hemorrhages resulting from the erosion of vessels are rare, but perforation into a neighboring organ is more frequent. In spite of the fact that some patients succumb to a radical operation, this intervention deserves a wide application, because all palliative operations are of slight value. They prolong life for only a few months, during which the patient suffers intensely. In the presence of ileus a fistula must first be made. The operation is thus performed in three stages. In carcinoma of the transverse colon and of the loop of the sigmoid, the Mikulicz method of exteriorization can be successfully employed. In carcinoma of the colon on the right side (cecum, ascending colon, hepatic flexure and right transverse) the one stage operation is the method of choice.

Ugeskrift for Læger, Copenhagen

102:1081-1104 (Oct. 17) 1940

*Peripheral Facial Hemispasm and Its Treatment. H. Jessen.—p. 1081.
Case of Polyneuritis after Intoxication at Work with Calcium Nitrate. A. Ibsen.—p. 1084.
*Treatment of Acute Otitis Media with Sulfapyridine (Preliminary Report). B. R. Hansen.—p. 1087.
Experiences with Chemotherapeutic Treatment of Acute Otitis Media. C. C. Bager.—p. 1091.
*Effect of Sulfapyridine in Some Cases of Leukemia. P. Plum and J. K. Poulsen.—p. 1093.
Sulfapyridine Treatment in Case of Leukemia. J. Bang.—p. 1095.
Case of Vaccine Pustules on Eyelids Treated with Sulfapyridine. V. Larsen.—p. 1096.

Peripheral Facial Hemispasm.—According to Jessen, peripheral facial hemispasm is a well defined disorder depending on irritation of the facial nerve. When in some cases an etiologic agent can be established it is most often a tumor of the cerebellopontile angle, but in most cases the disorder is cryptogenic or autonomic. Treatment consists in paralyzing the nerve with diluted alcohol. In grave cases in which the whole nerve area is affected the nerve must be attacked at the stylomastoid foramen by the anterior or the posterior route. In milder cases with localized spasms excellent results are obtained by paralyzing only the peripheral nerve branches at their issue from the parotid fascia. The picture of the disorder and treatment are illustrated by four cases, and the differential diagnosis is illuminated by one case of cortical origin (Jackson epilepsy) and one of psychogenic hemispasm.

Treatment of Acute Otitis Media with Sulfapyridine.—Hansen reports on the results of the treatment in 127 cases, with 130 nontreated cases as control. The drug seemed to him to have a certain favorable effect, especially in shortening the course in the patients who recover without operative treatment. No positive conclusion could be drawn concerning the patients operated on because of the small number. For the time being he advises against treatment of patients with acute uncomplicated suppuration of the middle ear with sulfapyridine in the practice because of the toxic effects.

Sulfapyridine in Leukemia.—Plum and Poulsen administered sulfapyridine to 2 patients with chronic myeloid leukemia, 2 with acute lymphatic leukemia and 1 with chronic lymphatic leukemia. A transitory improvement in the general condition and the blood picture was seen in the 2 cases of acute lymphatic leukemia.

102:1129-1156 (Oct. 31) 1940

Chronic Carbon Monoxide Intoxication: Review and Cases. F. Bom.—p. 1129.
Three Cases of Carbon Monoxide Intoxication. K. Hermann.—p. 1133.
Scabies Morbidity and Treatment of Scabies in Denmark. V. Genner.—p. 1135.
*Case of Leptospirosis Canicolaris with Marked Nephropathy. N. Bukh.—p. 1142.
Mild Cases of Leptospirosis (Weil's Disease). I. Knudsen.—p. 1146.
Anaphylactic Shock after Injection Treatment of Varices with "Varicocid." A. Bertelsen.—p. 1147.
Treatment of Eczema. P. Levison.—p. 1148.
Fracture of Lesser Trochanter: Rare Fracture—How Rare? A. Stefansson.—p. 1148.

Leptospirosis Canicolaris with Nephropathy.—The nephritis in Bukh's case was characterized by true uremia, incipient anuria and pronounced impairment of renal function for a long time. The grave nephropathy is ascribed to the canicolar infection. Two months after discharge examination of the patient showed complete restoration of the kidney function.

Book Notices

New Facts on Mental Disorders: Study of 89,190 Cases. By Neil A. Dayton, M.D., M.C., Director, Division of Statistics and Director, Division of Mental Deficiency, Massachusetts State Department of Mental Health, 1926—. Cloth. Price, $4.50. Pp. 486, with illustrations. Springfield, Illinois, & Baltimore: Charles C. Thomas, Publisher, 1940.

The Massachusetts State Department of Mental Health has had in Dr. Dayton, the author of the present work, a student of statistics of mental diseases who has produced a mass of material previous to this book and in this volume a mass of statistics which is beyond easy assimilation. The modern mental hygiene system of Massachusetts has permitted the collection of statistics on all patients admitted to mental hospitals and other mental institutions between the years 1917 and 1933. There are 56,579 first admissions in this group, and other groups of cases being the total number of cases studied to 89,190. During this period the first World War, prohibition and repeal, and the depression entered into the picture. Most of the material has been tabulated and graphed. There are 110 graphs. The main topics which are considered are age and mental disorders, nativity and alcoholism not only in mental disorders but with regard to other factors such as sex and marital status. Marriage as a factor is reported, and clinical diagnosis is a principal point which is included. The reader going through this volume is amazed at the number of preconceived ideas of mental disorders which are exploded by Dr. Dayton's valid statistics. Each of these factors is broken down into as many subgroups as possible; for instance, under marriage the group is divided into rural and urban. There is a religious subgrouping; veterans are compared with nonveterans, the foreign born with native born, the length of time in the United States and other countries. The multiplicity of features leads one to believe that it will be a long time before there is a more thorough study ever made to cover this subject. The ratio of divorces and separations to the total number of marriages and the two combined with regard to education and literacy does not carry with it a comparable table or interpretation. After each table and graph there is a chart discussion. The author goes into the matter at the end of some chapters with a good interpretation of the whole picture. It is interesting to note that the author has a summary at the beginning of the chapter instead of at the end, and this might be a valuable precedent. The book is to be recommended to all those who wish to get a picture of the mental patient who is hospitalized and particularly those *en masse*. It should be full of ammunition for writers on the subject of marriage, alcoholism, sex and mental diseases for some time to come.

A College Textbook of Hygiene. By Dean Franklin Smiley, A.B., M.D., Medical Adviser and Professor of Hygiene in Cornell University, New York, and Adrian Gordon Gould, Ph.B., M.D., Assistant Medical Adviser and Assistant Professor of Hygiene in Cornell University. Third edition. Cloth. Price, $2.50. Pp. 539, with 135 illustrations. New York: Macmillan Company, 1940.

The first edition of this textbook appeared in February 1928 and a second edition followed in 1934. The present volume is quite up to date and is sufficiently complete to serve as a source of information not only on public health but also on personal health. Indeed, it is aimed primarily as a guide for students as well as a book of instruction in classes. The experiences of the authors as medical adviser and assistant medical adviser in Cornell University give them practical experience on which to base their recommendations. Some of the points which they make have great practical value for every physician. For instance, as a result of their observation of food ordered by students in university cafeterias it was noted that among the chief faults in the selection of food was excessive use of meat, white bread and potatoes, lack of coarse bread, lack of vegetables at the noon meal and a lack of variety of cooked cereals, also poorly cooked and poorly flavored vegetables, too few salads, no variety of fruit at breakfast and a provision of skimmed milk only for drinking purposes. Obviously a little reform in the direction of education regarding diets for students would be a great step toward aiding the national campaign for physical fitness. An especially interesting chapter is the one entitled "You and Your Doctor," which explains why every one should have a private physician and go to him periodically for examination and advice. One of the best sections here is that on choosing a physician. There is a good statement of the advantages and the disadvantages of the fee for service system and of various technics which have been developed for changing the nature of the practice of medicine. The authors feel that it would appear to be sound procedure to conserve the values that are proving to be inherent in our present scheme of fee for service in medical practice and at the same time to make every effort to remedy its most glaring defects. They offer some suggestions toward improvement. The suggestions are sound. They are based on a reading and an understanding of much of the literature which has appeared on this subject in recent years. This book is supplemented by a good glossary of technical terms and may be heartily recommended as one of the best textbooks available in this field.

Men at Their Worst. By Leo L. Stanley, M.D., Chief Surgeon, California State Prison, San Quentin. With the collaboration of Evelyn Wells. Cloth. Price, $3. Pp. 322, with 24 illustrations. New York & London: D. Appleton-Century Company, Incorporated, 1940.

For twenty-seven years Dr. Leo L. Stanley has been chief surgeon of the California State Prison at San Quentin. Here he came in contact with many a notorious criminal. He has observed the coming of scientific advancement in the conduct of prisons and has himself experimented widely with plastic surgery, glandular technics and similar problems. In his conclusion he points out that his twenty-seven years of observation have given him no definite conclusions as to prevention of crime through education. In his glandular experimentation he has done over 10,000 testicular implantations and believes that there is a place in the medical management of prisoners through a study of the endocrines. The volume makes an interesting book of reminiscences but is not well organized and does not represent much in the way of a scientific contribution to the questions involved in the care of criminals.

Recent Advances in Sex and Reproductive Physiology. By J. M. Robson, M.D., D.Sc., F.R.S.E. With introduction by Professor F. A. E. Crew, M.D., D.Sc., F.R.S., Director of the Institute of Animal Genetics, Edinburgh. Second edition. Cloth. Price, $5. Pp. 329, with 62 illustrations. Philadelphia: Blakiston Company, 1940.

This edition indicates the rapid progress made in our understanding of the action and uses of hormones and substances having hormone-like actions related to reproduction. Since 1934, when the first edition appeared, a number of crystalline compounds have been isolated from the various endocrine glands, particularly the gonads and the adrenal cortex, and others with similar properties have been prepared in the laboratory. Our knowledge of the physiologic action of these compounds has thereby been cleared of much confusion resulting from experimentation with crude and relatively inactive extracts of glands. Furthermore, numerous crystalline compounds for therapeutic use have also been made available. Following these developments, innumerable reports have appeared in the past few years on the clinical uses of such substances, studies on their excretion and their metabolism in animals. The literature on these advances has become so vast that the average physician is usually unable to keep abreast of it, and even the specialist has difficulty in digesting the mass of writings. For this reason Robson's monograph is of distinct value. The author has selected a large number of articles from the scientific literature of the world and has evaluated their contents critically and with imagination indicating that the author, who himself has contributed greatly to our knowledge of the endocrines, understands keenly the problems and questions which are most pertinent at the present time. In this manner the reader will be in a position to attain a clear picture of the newer developments in the field. In this book there is discussed systematically the nature of the sex cycle, the histologic changes of the sex organs, the relationship of the various glands to one another, the chemistry, physiology and standardization of the various endocrine principles and the applications of the various preparations to clinical problems. This book is valuable to the physician in giving him an understanding of the principles of therapy and it is also recommended to the physiologist as a means of surveying the recent literature in the field of reproduction.

Methods for Diagnostic Bacteriology: A Complete Guide for the Isolation and Identification of Pathogenic Bacteria for Medical Bacteriology Laboratories. By Isabelle G. Schaub, A.B., Assistant in Bacteriology, Department of Pathology and Bacteriology, The Johns Hopkins University School of Medicine, Baltimore, and M. Kathleen Foley, A.B., Bacteriologist in Charge of the Diagnostic Bacteriological Laboratory of the Medical Clinic, The Johns Hopkins Hospital, Baltimore. Cloth. Price, $3. Pp. 313. St. Louis: C. V. Mosby Company, 1940.

This book is a manual of methods in diagnostic bacteriology written principally for interns, medical students and student technicians. The book is divided into three parts: The first part is concerned with bacteriologic diagnosis and consists of six chapters, the second part deals with serologic diagnosis and is divided into two chapters, while the third part is concerned with mediums, stains and staining technic, reagents and tests and is composed of three chapters. There are no illustrations, and only one side of the page contains printed matter, leaving the other side for notes. There are no theoretical discussions or explanations, the material being confined to explicit instructions. Many tables are included in which related organisms are differentiated. The book should prove very useful to diagnostic laboratories and to the group for which it was written.

The Organism: A Holistic Approach to Biology Derived from Pathological Data in Man. By Kurt Goldstein, M.D. With a foreword by K. S. Lashley. American Psychology Series. Henry E. Garrett, General Editor. Cloth. Price, $4. Pp. 533. New York: American Book Company, 1939.

Previous to the present régime in Germany, Kurt Goldstein was considered the leading pathologist in the country. His laboratory in Frankfort contained a mass of serial sections of the nervous system from the elephant down to the smallest of animals. He had considerable experience in working with traumatic cases in the first World War. After leaving Germany he paused for a short while in the Netherlands, where he wrote the present volume. Then he came to the United States, and his book has been translated into excellent English. In brief, it is a complex but basically sound summary of the general belief about the functioning of the central nervous system. Goldstein believes that the reflexes and other similar concepts of nervous activity cannot be taken out of the theoretical context but that the organism must be thought of as a whole. The point of view is broadly biologic. The clinical material and the research material are included to illustrate points. A number of new concepts are brought out, supported well, such as dedifferentiation, organism as a constant, and life and mind antagonism. It is a splendid, deep and complex study directed toward the psychologist, and undoubtedly of value to the physician or scientist who has to deal with problems of organic neurology.

The Streptococci: Their Descriptions, Classification, and Distribution, with Special Reference to Those in Milk. By William D. Frost, Ph.D., Dr.P.H., and Mildred A. Engelbrecht, Ph.D., Assistant Professor of Bacteriology, University of Alabama, University. Cloth. Price, $4.25. Pp. 172, with reproductions of 120 photomicrographs. Madison, Wis.: Willdof Book Company, 1940.

This book contains reports of the investigations which Dr. Frost and his associates have made over a period of many years. The work was supported by the certified milk interests in the Chicago and Milwaukee areas and involves the bacteriologic examination of upward of 25,000 samples of milk drawn directly from the cow's udder. The samples of milk were plated in blood agar and the streptococci present isolated and identified. The methods used in the study are discussed at length in the book. Much space is wasted in the reproduction of photomicrographs of different colonies of streptococci which morphologically are indistinguishable. The book should prove of interest to dairy bacteriologists and to health officers, as well as to veterinarians.

The Virus: Life's Enemy. By Kenneth M. Smith, F.R.S. Cloth. Price, $2. Pp. 176, with 20 illustrations. New York: Macmillan Company; Cambridge: University Press, 1940.

More and more the viruses are beginning to be recognized as important agents in the causation of disease. Now that smallpox, measles, infantile paralysis, influenza and many other important conditions are being recognized as of this etiology, the public should have an understanding of the nature of viruses at least as good as that which they have of bacteria. These viruses seem to exist midway between the living and the nonliving. They are spread by carriers, both human and insect in type. They are found as infections of plants and lower animals as well as of man. They vary in their virulence and they seem to be undergoing an evolution which brings them into new diseases such as encephalomyelitis. This volume, prepared primarily for a public audience, will do exceedingly well as a source of information for physicians who have not done much to keep abreast of our advancement in this field. It is written excellently and succinctly. It includes a table of the various important virus diseases and a good index.

The Head and Neck in Roentgen Diagnosis. By Henry K. Pancoast, M.D., Eugene P. Pendergrass, M.D., Professor of Radiology and Director of the Department of Radiology, University of Pennsylvania, Philadelphia, and J. Parsons Schaeffer, M.D., Ph.D., Professor of Anatomy and Director of the Daniel Baugh Institute of Anatomy, Jefferson Medical College, Philadelphia. Cloth. Price, $12.50. Pp. 976, with 1,251 illustrations. Springfield, Illinois & Baltimore: Charles C. Thomas, 1940.

This richly illustrated book deals with the x-ray appearance of the normal head and neck and the x-ray diagnosis of practically all the known anomalies, diseases and injuries of these structures. The book is noteworthy for completeness, clarity and the skill with which the important has been emphasized, the rare, and therefore relatively unimportant, minimized and yet not neglected. Intracranial tumors and the making and interpreting of cerebral pneumograms receive the extensive consideration that their clinical importance requires. The rather large amount of space devoted to the soft tissue structures in the neck is justified by the current interest in this subject and the special qualifications of these authors to speak on it. One looks in vain for sections, chapters or even pages carrying evidence of perfunctoriness, padding, ambiguity, stinginess in indexing, inadequacy of legends or other common faults of medical writing and publishing. Reviewers will find it difficult to employ conventional restraint in describing this altogether spendid and unusual book.

Medical Work on the Knights Hospitallers of Saint John of Jerusalem. By Edgar Erskine Hume, Lieutenant-Colonel, Medical Corps, United States Army. Foreword by His Most Eminent Highness Fra Ludovico Chigi-Albani, Prince Grand Master of the Sovereign Military Order of Malta. Preface by Lieutenant-General Sir Aldo Castellani, K.C.M.G., Count of Chisimaio, Professor at the Universities of Rome, London and Louisiana. Reprinted, with additions, from the Bulletin of the Institute of the History of Medicine, May, June and July 1938. Cloth. Price, $3. Pp. 371, with 131 illustrations. Baltimore: Johns Hopkins Press, 1940.

The Knights of Saint John are a band of Christians who founded a hospital in Jerusalem for the care of the poor and pilgrims. During the Crusades they were driven from the Holy Land and established themselves as an order from Cyprus, Rhodes and Malta. The patron saint of the order was Saint John the Baptist. Among other items in their work is the care of leprosy for the natives of Ethiopia, aid to the wounded in Spain and, indeed, the provision of medical organizations of volunteers in all wars. This record of their contribution is a carefully detailed account illustrated with more than a hundred photographs and supplemented with a good bibliography and an index. For nine centuries this organization has rendered distinguished service in the care of the sick. Colonel Hume's account is a fine contribution to the history of Saint John.

Principles of Surgical Care, Shock and Other Problems. By Alfred Blalock, M.D., Professor of Surgery, Vanderbilt University School of Medicine, Nashville, Tenn. Cloth. Price, $4.50. Pp. 325, with 13 illustrations. St. Louis: C. V. Mosby Company, 1940.

The problem of making the patient safe for the operation, as Moynihan expressed it, has been yielding slowly to the unremitting assault of many scientists. The ability to evaluate the condition of the patient in laboratory as well as clinical terms has been of great service in reducing surgical morbidity and fatality. This monograph is an extension and amplification of the Beaumont Lectures for 1940. It emphasizes that operation is only part of the treatment of surgical patients. The author has presented well correlated and well digested material. The subjects include the importance of anesthesia and careful surgical technic as well as longer discussions on the circulatory and metabolic systems. The theories of shock and the various associated deficiencies of the circulatory constituents and contents receive ample consideration. Plenty of bibliographic references are included. The book is an enlightening report of the care which a modern surgeon can offer along with his skilful technic and judgment at the operating table.

Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

PERSISTENT PAIN FOLLOWING HERNIA REPAIR

To the Editor:—**Four months ago I operated on a 55 year old man for a right direct inguinal hernia. After ligating and amputating the sac, I sutured the conjoined tendon to Poupart's ligament along with the medial flap of the external oblique fascia under the cord and imbricated the lateral flap over the cord. He was in bed for two weeks, and shortly thereafter he began to complain of pain, usually sharp and sometimes radiating to the inner aspect of the thigh. At no time was there induration of the cord or swelling of the testis. After I injected procaine hydrochloride solution in the region of the cord just lateral to the pubic tubercle, this point being the distal end of the incisional scar, the pain and tenderness disappeared, only to reappear after the anesthesia wore off. Believing that the nerve which accompanies the spermatic cord might be caught in a ring of scar tissue, I reopened the wound and dissected free the cord, the nerve and its branches at the distal end of the old herniorrhaphy scar. This failed to relieve his symptoms. There is no evidence of recurrence of the hernia. What is the cause of the pain and how can it be remedied?** M.D., Michigan.

ANSWER.—The report of this case seems to indicate a scar or ligature compression of a peripheral sensory nerve, despite the fact that at the second operation a nerve was seen to be free. In this region one deals with two nerves, the iliohypogastric and the ilioinguinal. Callander (Callander, C. L.: Surgical Anatomy, Philadelphia, W. B. Saunders Company, 1934, p. 407) said, "The iliohypogastric nerve runs forward in the abdominal wall near the superior margin of the iliac crest, and there divides into hypogastric iliac branches. The hypogastric branch continues forward to a point about 2.5 cm. above the subcutaneous inguinal ring, where it pierces the aponeurosis of the external oblique and is distributed to the skin of the hypogastric region. The iliac branch crosses the iliac crest and is distributed to the skin of the forepart of the gluteal region. The ilioinguinal nerve enters the region at a somewhat lower level than the iliohypogastric and, after crossing part of the iliac fossa, enters the inguinal canal. It runs anteriorly beneath the aponeurosis of the internal oblique immediately above the inguinal ligament and emerges from the subcutaneous inguinal ring." A case similar to this is known in which the man walked with a list to the side because of the pain and had been given orthopedic treatment. He was not cured until the nerve was dissected free of the scar tissue. In the case referred to in the query one would certainly think that further exploration of the wound is desirable until both ilioinguinal and iliohypogastric nerves are identified and traced to their extreme ends. If it is not possible to free the distal branches of the affected nerve, it would probably be better to section it high and possibly inject it with alcohol.

EXPOSURE TO SYPHILIS

To the Editor:—**A man with a fresh chancre diagnosed by dark field had intercourse a week ago without prophylaxis or contraceptives being used. What is the best procedure now in reference to the woman? Should treatment be instituted immediately with her and how much, or should her vaginal tract be inspected daily until the appearance of the expected chancre and then treatment started? I realize that starting treatment without definite evidence of infection is forever labeling her as syphilitic whether she would have been or not. Presumably she now has a negative Wassermann reaction, which test has been taken.** M.D., New York.

ANSWER.—The proper procedure in the case outlined depends, of course, on the probability of the woman having become infected with syphilis. Were she certain to become infected one could make a good case for the immediate institution of antisyphilitic treatment, arguing that since treatment results are known to be best in the seronegative primary stage they should be even better in the seronegative stage before the primary lesion has developed. Under the circumstances detailed, however, infection of the woman is by no means certain. This would be true even if the penile lesion which was found to be darkfield positive had been present at the time of intercourse; one gathers, however, that the penile sore developed after the last intercourse with the woman, in which case her chances of escaping infection are excellent. She should be carefully observed both clinically and serologically; at the first examination the cervix should be inspected through a speculum, in addition to a close scrutiny of skin, mucosal surfaces and genitalia. The procedure from this point on would depend somewhat on the time at which the patient came under observation, since the desirable maneuvers are related to the date of her exposure.

From this date she should have a serologic test for syphilis done at two, four, five, six, seven, eight, nine, ten and twelve weeks, assuming of course that it continues to give negative results and finally, before being discharged from observation, a final test four months after exposure. If at all practical, a complete inspection including a speculum examination is highly desirable but is urgently necessary only in the first few weeks when there is the opportunity to make the diagnosis of syphilis in the seronegative stage, in case she has acquired the disease.

This is the setup for the use of the so-called prophylactic dose of arsphenamine, which is a dangerous and fortunately outmoded procedure. Actually to administer any antisyphilitic treatment to this woman would, for safety, necessitate the completion of the entire schedule of treatment for seronegative primary syphilis, just as though that diagnosis had been made.

ADDICTION TO PAREGORIC

To the Editor:—**Seven years ago a man who is now 33 years old was in an automobile accident and, as a result, afterward suffered from frequent headaches. It was because of the severity of these headaches that he began to take paregoric. He had also a 4 plus Wassermann and has taken treatments for about ten weeks. In the beginning he started with 2 ounces of paregoric each day, gradually increasing the amount until he was taking a pint a day. Two years ago he started to inject the paregoric by boiling the alcohol off and then straining it through cotton, using an eye dropper and a needle for the injection. By this method he has ruined every vein in his arms and legs. He has gone to many different drug stores and is now unable to obtain paregoric from any one of them. He says he can get along fairly well with 4 oz. (120 cc.) daily, that is, 1 ounce (30 cc.) per dose, but is unable to obtain even that amount. In order to fight the habit he has tried to become a drunkard, but alcohol alone has had little effect. He has also tried pentobarbital sodium, having taken it intravenously, but after ten minutes' sleep he wakes feeling worse. At present he can walk only about 20 to 30 feet and is then forced to rest because of shortness of breath. This man is anxious to overcome the habit. He would like to take antisyphilitic treatments.** M.D., West Virginia.

ANSWER.—The underlying causes of narcotic addition are in the personalities of the addicts. No person is immune to opiate addiction. Morphine administered to any hundred persons will in time produce abstinence symptoms and make 100 addicts. However, there are two major types of personalities, the potential and the nonpotential narcotic addict. There are many persons who are unsuspecting potential narcotic addicts, who get along well until narcotic drugs come into their lives. The ones who do not succumb are not always the stronger willed; but the excessive indulgence holds no appeal to them, and often they get more pain than pleasure from it, so the experience is not repeated. One should avoid repeating the dose of opiate when great relief is given or more than an anodyne effect is secured, especially in neurotic patients. More than 75 per cent of the addicts seen today who do not belong to the vicious type are made up of the inadequate personalities who are unwilling or think they are unable to stand physical or mental stress without the relief of narcotism. The patient in question is definitely a potential addict who either is of the vicious type or who has been associating with such people to the extent that he has adopted their methods. A normal accidental addict does not inject paregoric, use an eye dropper and a needle and resort to intravenous injections to obtain a greater "kick," ruining every vein in his arms and legs and using greater amounts than are necessary.

The fact that the patient does not care for pentobarbital sodium or alcohol means that he is unwilling to accept a weaker substitute for his accustomed opiate. Syphilis does not need narcotic relief. This patient can be successfully denarcotized at any reputable institution where narcotic patients are accepted; those in charge will ascertain whether he has a really incurable disease that necessitates narcotics, and if not they can, after disintoxication treatment, attempt to rehabilitate him if he has the financial means. However, from the history the prognosis is unfavorable. If the patient's means are limited an institution nearby similar to the Narcotic Farm at Lexington, Ky., offers the best chance of a favorable outcome.

ADHESIVE FOR CIGARET PAPERS

To the Editor:—During a discussion of cigarets and their composition some one mentioned the fact that the paste which glues the cigaret paper together might be harmful. Could you inform me as to the composition of the substance used to paste the cigaret paper together and if it is at all harmful? B. B. Favuzza, M.D., Franklin Square, N. Y.

ANSWER.—Although some types of cigarets, such as the hollow stemmed East European varieties, are made without paste, by crimping the paper along the edge, and others may use dextrin, starch or similar vegetable pastes, by far the greater number, including almost all of the popular American blends, are made with the use of an adhesive made of casein, the protein obtained from milk. The products of combustion or destructive distillation of this protein include ammonia and other nitrogenous substances, which may be irritating in high concentration. The extremely minute amount of the material used in the production of cigarets, however, compared with the amount of tobacco and paper present, makes it impossible to detect any differences in the composition of the smoke due to the presence or absence of the adhesive. There is no evidence therefore and, in fact, little possibility that the substance used to paste the cigaret paper together is at all harmful.

FACE MASKING IN NEWBORN NURSERIES

To the Editor:—Will you please make a statement as to the status of "nurse masking" in the nursery? How generally is it practiced? Does the Chicago Board of Health require it in Chicago hospitals? Would a hospital not employing such masking be legally liable for contagious spread through the respiratory system affecting its nursery patients? E. D. Huntington, M.D., Chicago.

ANSWER.—The rules and regulations of the Chicago Board of Health for maternity hospitals require that nurses, physicians and all others entering the newborn nursery wear a suitable face mask all year, except during the summer months; these rules are strictly adhered to by Chicago hospitals. During the summer months, the wearing of face masks by the nursing and other personnel is optional.

The fixing of legal responsibility, in instances in which infection of the respiratory tract spreads through the nursery, would require thorough investigation and often would be impossible to establish. Obviously, if any of the personnel are suffering from such an infection they should not be permitted to work in the nursery. If they do not have an active infection of the respiratory tract it would be difficult to demonstrate the failure to wear a face mask as responsible for an outbreak of respiratory disease.

ABDOMINAL DISTENTION IN DIABETIC GIRL

To the Editor:—A diabetic girl aged 14 years was hospitalized four weeks ago and the blood sugar was brought from 400 mg. to 120 mg. by use of a 1,650 calory diet made up of protein 80 Gm., fat 90 Gm., carbohydrate 135 Gm. and insulin. She was discharged from the hospital after two weeks on this diet and insulin (regular 40 units to the cubic centimeter), 35 units before breakfast, 20 units before lunch and 30 units before dinner. Two days later she complained for the first time of abdominal distention, which was extreme and caused moderate embarrassment of breathing. The gain in weight was 13 pounds (6 Kg.) in two weeks. Except for this condition she felt much better than previously and her appearance was much improved. There was no complaint of distention while she was in the hospital bed. Several days later a complete gastrointestinal examination was done and was negative. Chest x-ray films showed slight hypertrophy of the heart. The pulse ranges from 104 to 114 per minute and is regular in rate. The heart sounds are normal and the rate is regular. The lungs are normal to physical and x-ray examination. Abdominal examination reveals a generalized and extreme distention which is tympanitic in character; there are no masses or tenderness. The bowels are regular, and spontaneous daily movement occurs. Urine examination is negative except for sugar, which ranges from 1 plus to 2 plus with occasional negative tests in the morning. There is no evidence of edema. She complained once of dimness of vision but this cleared up. The thyroid is normal in size. Urinary output and intake balance normally. In the morning there is little or no distention on arising but it gradually increases during the day to a maximum in the evening. At the night meal she feels "too full to eat," although she does eat the prescribed diet. The diagnosis of diabetes mellitus was first made by another doctor six months ago and insulin was taken in approximately the same dosage as at present for three months. During the period insulin was taken the same distention occurred and persisted in spite of all treatment until insulin was stopped. There was no distention present during the period when no insulin was taken. I have exhausted all possibilities that I know of in trying to determine the cause of this condition. I have been unable to find a parallel case in the medical records indicating any relation between large doses of insulin and abdominal distention. Any help that you might give me would be greatly appreciated. M.D., New York.

ANSWER.—Several possibilities suggest themselves as the cause for the unusual abdominal distention:

1. The condition is reminiscent of that seen when diabetic children received bulky diets, especially those containing bran along with large amounts of leafy green vegetables. Is it possible that at home the patient takes additional food, particularly in the form of broth or between-meal lunches? If she was using certain diabetic candies and diabetic cookies she might be receiving a good deal of bran or agar agar.

2. Does the patient swallow air during rapid eating?

3. Can the condition be related to the rapid gain of weight, 13 pounds in two weeks, incident to bringing the diabetic condition under control? This implies retention of water in a body previously dehydrated and, since there is no peripheral edema ("insulin edema"), one wonders whether there may not be some fluid in the abdomen.

4. It is difficult to believe that the distention and attendant gastrointestinal symptoms represent an unusual type of allergic response to insulin, particularly since no other manifestations of hypersensitiveness are described.

5. In juvenile patients with severe diabetes who are maintained entirely on regular insulin (without protamine zinc insulin) it is not uncommon to have marked enlargement of the liver with abdominal distention, which at times may be so great as to give rise to a "pot-belly" habitus. The liver may be difficult to feel on physical examination but should be evident by x-ray examination. In the case under discussion it is possible that this manifestation of disturbed metabolism became evident only when there was retention of water in the liver following institution of treatment with insulin.

6. The possibility should be kept in mind that the abdominal distention is due to some cause entirely apart from diabetes, such as a megacolon, abdominal tuberculosis or vitamin deficiency. Why should the heart show "slight hypertrophy" and why is there tachycardia?

Extensive studies have already been carried out. One can suggest only that the patient be kept under close watch so that other observations as regards both diabetic and nondiabetic complications can be made. It is likely that shifting the patient to a combination of protamine zinc insulin and regular insulin, both types given daily before breakfast, would permit even better control of the diabetic condition.

DIGITALIS FOLLOWING STROPHANTHIN

To the Editor:—I am of course aware of the precautions necessary concerning the use of strophanthin when a patient has been receiving digitalis, but what I have been unable to find is information concerning the use of digitalis when a patient is receiving strophanthin. Is it possible merely to substitute a maintenance dose of digitalis when the strophanthin is discontinued or is digitalization necessary to the same extent as with a patient who has received no prior medication? M.D., Iowa.

ANSWER.—Since strophanthin is excreted more rapidly than digitalis, its cumulative effect is comparatively small. It is advisable, therefore, to start with higher than just maintenance doses of digitalis when therapy shifts from strophanthin given intravenously to digitalis given by mouth. However, the dose of digitalis chosen depends on the intensity of the previous treatment with strophanthin and the response to it. After a single dose of strophanthin, digitalization will be necessary to the same extent as when a patient has received no prior medication. When daily injections of strophanthin are given a high degree of "digitalization" can be obtained, and for patients receiving these it may be sufficient to continue with ordinary maintenance doses of digitalis administered orally. If intoxication occurs after intravenous strophanthin therapy, an interval of a few days should be allowed to elapse until the toxic manifestations have disappeared, just as is done after excessive digitalization, after which maintenance doses of digitalis can be resumed.

MICROSCOPIC DIAGNOSIS OF MALIGNANT TISSUE

To the Editor:—What are the principles of the microscopic diagnosis of cancer? Which is more important, the morphology of the cell or the architecture of the tissue? Why do skilled pathologists so frequently disagree in their diagnosis of tumor? In the textbooks of pathology which I have consulted but little information on this important subject can be obtained. M.D., Kentucky.

ANSWER.—The morphologic signs of malignant disease are variations in size and shape of cells, hyperchromatism of nuclei, and excessive mitotic activity. When these microscopic features occur among cells which still remain within normal boundaries the lesion is designated as precancerous or potentially cancerous. The criterion of fully established malignant disease is when cells having these morphologic appearances have transgressed their normal boundaries. Skilled pathologists disagree in their diagnoses of tumors because the microscope has definite limitations and because it is difficult to estimate the biologic character of a tumor from its morphologic appearance.